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CONTINUOUS PROPAGATION OF AMŒBIC DYSENTERY IN ANIMALS.

By Walter Albert Baetjer

and

Andrew Watson Sellards.

(From the Medical Clinic of The Johns Hopkins Hospital.)

OUTLINE.

I. Introduction and literature:
   1. Propagation of entamœbæ in animals is limited, as a rule, to three or four passages.
   2. General conclusions that the strain of entamœbæ dies out because of degeneration of the entamœbæ with consequent loss of virulence.
II. Method of transmission:
   1. Method of inoculation.
   2. Selection of infective material.
   3. Choice of animals with especial regard to age.
   4. Selection of suitable temperature and diluting agents in the handling of the infective material.
III. Behavior of a strain of dysentery on successive passage in animals:
   1. Effect on the clinical course.
   2. Effect on the entamœbæ.
   3. Effect of the accompanying bacteria.
IV. Relation of the entamœbæ to the general laws of the protozoan and bacterial infections.
V. Correlation of these data with previous results:
   1. Loss of strain by bacteriæmia in animals.
   2. Failure of infection on account of method of inoculation.
   3. Failure of infection on account of choice of material.
VI. Conclusions that passage in animals is not self-limited.

The infection of lower animals with amœbic dysentery presents some exceptional and complicated features, both in the variation in individual susceptibility and in the subinoculation from one infected individual to another, for the transmission of the disease through a series of animals. Amœbic infection with the reproduction of its characteristic symptoms has frequently been produced in several species of lower animals. Even under optimum conditions, however, the percentage of successful infections is extremely variable, ranging, with a few exceptions, from twenty-five to fifty per cent. The most unexpected feature develops upon subinoculation from animal to animal, when it is found that the infection invariably dies out. Werner[1] succeeded once in carrying a strain of entamœbæ, identified as hystolytica, through six passages. This limitation of the number of passages was explained on the basis of biological changes in the entamœbæ. Werner concludes that a strain becomes avirulent after a few passages to the extent that it not only does not produce symptoms, but apparently that it fails even to parasitize its host without producing symptoms.

Hartmann[2] found that the infection invariably died out in the second or third passage on account of degenerative changes which occurred in the entamœbæ. He concludes that kittens are naturally very refractory to infection. Wenyon[3] was also unable to carry a strain of dysentery further than four passages, but his conclusions differ radically from the preceding

observers. There was no evidence of any diminution in virulence and the strain was lost through accident. Wenyon concludes that it should be possible to propagate a strain of entamœbæ indefinitely in animals. Darling [4] has confirmed and extended Hartmann's observations. He concludes that the pathogenic entamœbæ not only become avirulent on passage, but that they undergo definite changes in their morphology and life cycle; the trophozoites diminish in size corresponding to *Entamœba minuta* and the tendency to encystment increases.

These authors, with the exception of Wenyon, distinguish carefully between two pathogenic strains: Namely, *Entamœba histolytica* (Schaudinn) and *Entamœba tetragena* (Viereck). Werner investigated several strains of entamœbæ and distinguished between histolytica and tetragena on the basis of morphological differences. As regards their biology, Werner could discover no constant differences either as regards their virulence, the number of passages that could be obtained in animals, the course of the disease in animals, and the pathological effects that could be produced. Hartmann's statements apply to *E. tetragena*. Darling, on the basis of Werner's results and his own experience, has emphasized more the difference in infecting power between the two types. According to him the histolytica-like strain can be carried as high as six passages, while the tetragena type rarely infects beyond two generations and often dies out in the first series of animals inoculated. The loss in virulence and infecting power in both types are, according to Darling, associated with definite morphological changes in the organisms, notably in the transformation which he has described as the "small generation," a form assumed by the organism in the generation before encystment occurs. Apparently there has been no attempt to propagate the parasitic but non-pathogenic *Entamœba coli*, and it is evident that the pathogenic entamœbæ have not been propagated except for a limited number of passages in lower animals. If one accepts that there are two species which are pathogenic for man, this statement applies equally well to either species. In 1911, however, Walker [5] reported observations which led him to conclude that two distinct species have not yet been established and that *E. histolytica* and *E. tetragena* are identical. He concludes that the morphological differences in the vegetative state in *E. histolytica* and *E. tetragena* which were originally described by Viereck [10] and Hartmann are extremely inconstant and that both of these types form their propagative stage in the same manner, *i. e.*, by the production of a four nucleated cyst. The reproduction by the process of budding, which, according to Schaudinn's description, occurs in histolytica, was not observed by Walker. The identity of these two species has since been accepted by Craig,[6] Wenyon,[3] and in its essentials by Hartmann [7] and by other observers. It seems to us that the evidence for the establishment of *E. tetragena* as a distinct species is wholly insufficient. Accordingly, we shall tentatively use the term *E. histolytica* of Schaudinn to include the four nucleated propagative stages discovered by Viereck until the nomenclature is definitely established. Hartmann [7] has recently suggested that the terminology should properly revert to that suggested by Councilman and Lafleur.[8] In case strains of *E. histolytica* with characteristically distinct propagative stages should be established, it might be desirable to retain the term "tetragena" to indicate a variety of *E. histolytica* but not as a distinct species of entamœbæ.

The determination of whether the propagation of amœbic infection in lower animals is self-limited becomes of interest from several standpoints. It is naturally of importance in the determination of the laws of protozoan infection and immunity. Moreover, in the absence of any methods for cultivating either the pathogenic or parasitic entamœbæ, the infection of animals is extremely desirable in order to obtain a suitable supply of material for study. This applies not only to the localities where acute cases are rare, but also to the endemic areas in the tropics. The infection of animals is so uncertain that only a minimum of experimental work has been done upon morphology, pathogenesis, and experimental therapy.

Methods of Transmission.—In attempting the propagation of a strain of dysentery in animals, the literature indicates that the routine of various workers has been fairly uniform. Accordingly, we have followed the usual technique as closely as feasible. Cats or kittens were selected. In the choice of the various routes of infection, we did not have occasion in this series to make use of feeding experiments. The majority of animals were inoculated by rectal injection. However, in order to secure the first transfers from man to lower animals, the infective material was injected directly into the cæcum. A small incision was made in the abdominal wall, the syringe needle was inserted through the wall of the cæcum, and the injection was made directly into the lumen. This procedure gave distinctly better results than were obtained, even under the most favorable conditions, by other methods of injection. The explanation for the high percentage of infections which was obtained probably depends upon a number of minor factors. Other strains of entamœbæ are under investigation at present and the discussion of this procedure will be reserved for a subsequent communication.

The first strain of dysentery with which we worked occurred as an initial attack in a negro, who had contracted dysentery in North Carolina with a history of three months duration. Duplicate injections of about 3 cc. each of a bloody mucous stool rich in trophozoites were made into the cæcum by laparotomy, in an adult cat and a half-grown kitten. After an incubation period of seven days, both animals became acutely infected. The adult cat developed a mucous diarrhœa with very large amœbæ and death resulted after sixteen days. The kitten showed a bloody dysentery with smaller organisms, and lived for nineteen days. Subinoculations were made from both animals immediately after death by injections into the cæcum in four animals. In all four death occurred promptly in one to five days from peritonitis, accompanied usually by septicæmia.

A little later a second case of dysentery was admitted to the hospital. This was an acute relapse, the original infection having been contracted in the Philippines a year and a half

previously. During the first fourteen months of the disease there had been several acute relapses with complete absence of symptoms in the interim. He was then treated with emetine and temporarily relieved. After four months he returned to the hospital in another acute attack. Emetine treatment was begun at once, and the patient had been receiving ⅔ grain, hypodermically, daily for three days before the stools were obtained from which the first animals were inoculated. In commencing the propagation of this strain especial attention was given to the following features:

1. Subinoculation from animal to animal at the first appearance of clinical symptoms in preference to waiting for the death of the animal or till the later stages of the infection.

2. Selection of suitable temperature and diluting agents in the handling of the infective material.

3. The selection of kittens (half-grown or younger) rather than adult animals.

4. The injection of the infective material directly through the lumen of the bowel into the cæcum in addition to the injections by rectal tube.

The details of this routine were comparatively simple. As far as possible the transfers were made at the first appearance of bloody mucous discharges in an infected individual. Only fresh material was used for injection. Usually not more than one hour elapsed from the time the specimens were obtained till the injection of all animals was completed. When the transfers were not made at the beginning of the infection the animals were usually sacrificed in preference to waiting for post mortem material. The contents of the lumen of the bowel when fæcal or purulent were discarded and amœbæ were obtained by scraping the mucosa of the intestine. In practically all cases the injected material consisted almost exclusively either of blood and mucus with little or no macroscopic contamination with fæces and with relatively few bacteria on microscopic examination. Trophozoites were present usually in large numbers in all the material which was injected and were not infrequently accompanied by an abundance of cysts. For the intracæcal injections it was found that relatively large pieces of mucus and blood could be forced through a needle of moderate bore, provided that no firm particles were present. When necessary, the material was suspended without emulsifying in tap water or in 0.2 per cent salt solution in tap water. Stronger concentrations of salt were deleterious. As far as possible the pieces of mucus were left intact, for it was found on microscopical examination that the amœbæ in vitro were preserved better in the fluid in which they occurred in the body than in any artificial solutions. The concentrations which were tried were tap water and solutions of technically pure sodium chloride in tap water of 0.1, 0.2, 0.3, 0.4 and 0.5 per cent dilution. The amœbæ in the specimens of blood and mucus from the intestine were best preserved without the addition of any foreign fluids. Of the diluting fluids 0.2 per cent salt was a little better than tap water alone and 0.5 per cent salt was the poorest. The optimum concentration of salt would probably vary within narrow limits according to the nature of the material in which the amœbæ were found. Furthermore, it was found that, in accordance with the preservation of other tissues, the amœbæ, though less active, retained their vitality better, at a room temperature of 20°C. than at incubator temperature.

Young animals proved to be distinctly more susceptible than adults. The youngest animals used weighed about 400 grams and these proved to be very suitable. The susceptibility varied directly with the age and we did not find that an optimum susceptibility occurred in kittens that were about half-grown as has been suggested. Injections directly into the cæcum were used more particularly for the injection of adult animals and in the early transfers. As the virulence increased, injection by high rectal tube proved to be more suitable than the intracæcal inoculations.

The following observations were kept as a routine:

1. Examination of the material which was injected by fresh and stained preparations.

2. Determination of the incubation period.

3. Observations upon the course of the infection in animals and when possible stained preparations of amœbæ obtained late in the course of the infection.

4. Determination of the occurrence of bacterial septicæmia with especial reference to the cause of death in fatal infections.

For the stained preparations the material was fixed by the wet method, and carried wet throughout the entire process of staining and mounting. The technique was essentially that used by Walker.[5] Smears were made by teasing out the material on cover slips without exerting any pressure. When the specimens were too viscous to spread in this manner, they were first teased out in a little tap water or in 0.2 per cent salt solution in tap water. These smears were floated at once face down on Zenker's fluid for five to ten minutes and then washed with one or two changes of water for several hours or over night in distilled water. They were then stained intensely in Delafield's hæmatoxylin for ten to thirty minutes and washed for several hours in tap water. This routine did not necessitate controlling the washing by microscopic examination. The stains were then cleared in alcohol (25-50-75 per cent and absolute) then in oleum origani vulgi and mounted in balsam.

The incubation period which is recorded is the clinical incubation period; *i. e.*, the time of appearance of definite clinical symptoms consisting in the passage of mucus and blood containing active entamœbæ. This seemed distinctly preferable to the determination of the earliest time at which entamœbæ could be identified microscopically in the stools, especially since with the extremely short incubation period which subsequently developed, and with the large injections in small animals, the appearance of entamœbæ in formed stools would be no proof that multiplication or parasitization had occurred. Moreover, the determination of the time of appearance of clinical symptoms was extremely satisfactory. The normal condition of the animals was very constant. In over 60 individuals which were kept under observation, the stools were regularly formed with the exception that in the very young kittens, six or eight weeks old, the stools were soft, but uniformly free from blood and mucus. After in-

oculation, the infection appeared as an acute outbreak characterized sometimes by a day in which one or more soft stools were passed, followed within a day by the discharge of both blood and mucus, and the presence of numerous active amœbæ. Whenever possible, this first discharge of blood and mucus was used for inoculation.

Blood cultures were made by aspiration from the heart according to the usual routine when the animals appeared ill, when they were sacrificed, or at the time of death. Septicæmia was encountered just before death in the majority of instances. In the early inoculations by laparotomy into the cæcum there was no difficulty whatever from peritonitis after the puncture of the cæcum even when a large syringe needle was used and the injected material was rich in fæcal matter. Subsequently, peritonitis became extremely difficult to avoid although the injected matter consisted macroscopically of blood and mucus and a small needle was used followed by careful cautery of the puncture wound.

Effect on the Clinical Course.—The general results which we obtained with this strain were somewhat unexpected. The entamœbæ, instead of losing their pathogenicity after several passages, increased remarkably in virulence. The incubation period in the four animals used for the first three passages was almost exactly six days with a duration of the disease lasting as long as six and a half weeks. These periods were shortened until in the sixth passage an incubation period of two and three-quarter days was obtained, with death occurring one day later. Not only did the virulence increase, but the trophozoites, instead of diminishing in size to the minute race which has been described, remained active and vigorous without any suggestion of degenerative changes. The strain became so active that it was not a simple matter to insure its continuation. A comparatively large number of animals were required to avoid absolutely the possibility of the loss of the strain through accident. On some occasions as many as six or seven animals were required to insure a single passage.

It soon became apparent that the changes in virulence and morphology which had been described as occurring constantly upon subinoculation of entamœbæ did not apply to this strain. When this was well established the number of animals used for any one passage was reduced to two or three. After eleven successive passages had been secured the strain was allowed to die out. All of the infected animals reacted typically—both clinically and pathologically; the morphology of the entamœbæ found in them was characteristic. The incubation period in the ninth, tenth and eleventh passages in a total of five animals ranged from five to nine days. This return to the longer incubation period was perhaps due in part to the continued passage of the strain by rectal injections rather than by direct inoculation into the cæcum, but also to the use of material taken several hours post mortem. The accompanying diagram (No. 1) shows some of the essential features of the successful inoculations.

Effect on the Entamœbæ.—Morphologically, the typical organisms show no degenerative changes either in fresh or stained preparations provided these are made from suitable characteristic specimens. This strain after passage through kittens showed no deterioration in the organisms in regard to size, motility, staining reactions, and structure of the nucleus. Encystment frequently occurred with the four nucleated cyst predominating, but the vegetative forms were always present in excess of the cysts. On the other hand, however, there were numerous opportunities for obtaining degenerated types corresponding to those described by Hartmann [l. c.] and by Darling.[l. c.] The organisms often became much less typical in chronic cases of long standing and in acute cases when bacterial complications developed such as a bacteriæmia or a purulent bacterial enteritis. Moreover, degenerative forms were frequently found in stools which, though freshly obtained, had often remained for some hours in the lumen of the intestine where the entamœbæ were extensively contaminated with fæces and were subject to bacterial fermentation and various deleterious influences. When such animals were sacrificed, typical entamœbæ were found higher up in the intestine or in the scrapings from the mucosa. In this connection it may be noted that some of the degenerations described by Darling occurred in specimens which were obtained post mortem. The accompanying plate illustrates typical specimens of organisms obtained from the patient, and from the eleventh passage in cats. Small degenerative forms occurring in the second passage are also included. Biologically, there was a definite increase in the virulence of this strain which was shown principally by the progressive shortening of the incubation period in the successive passages.

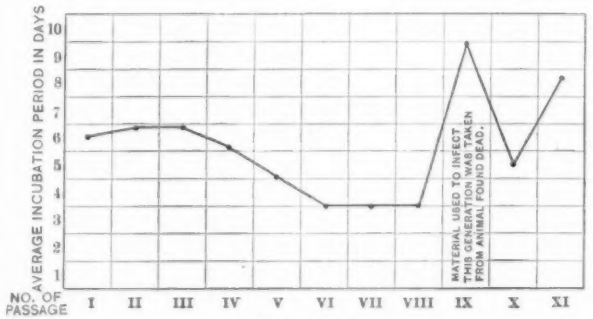
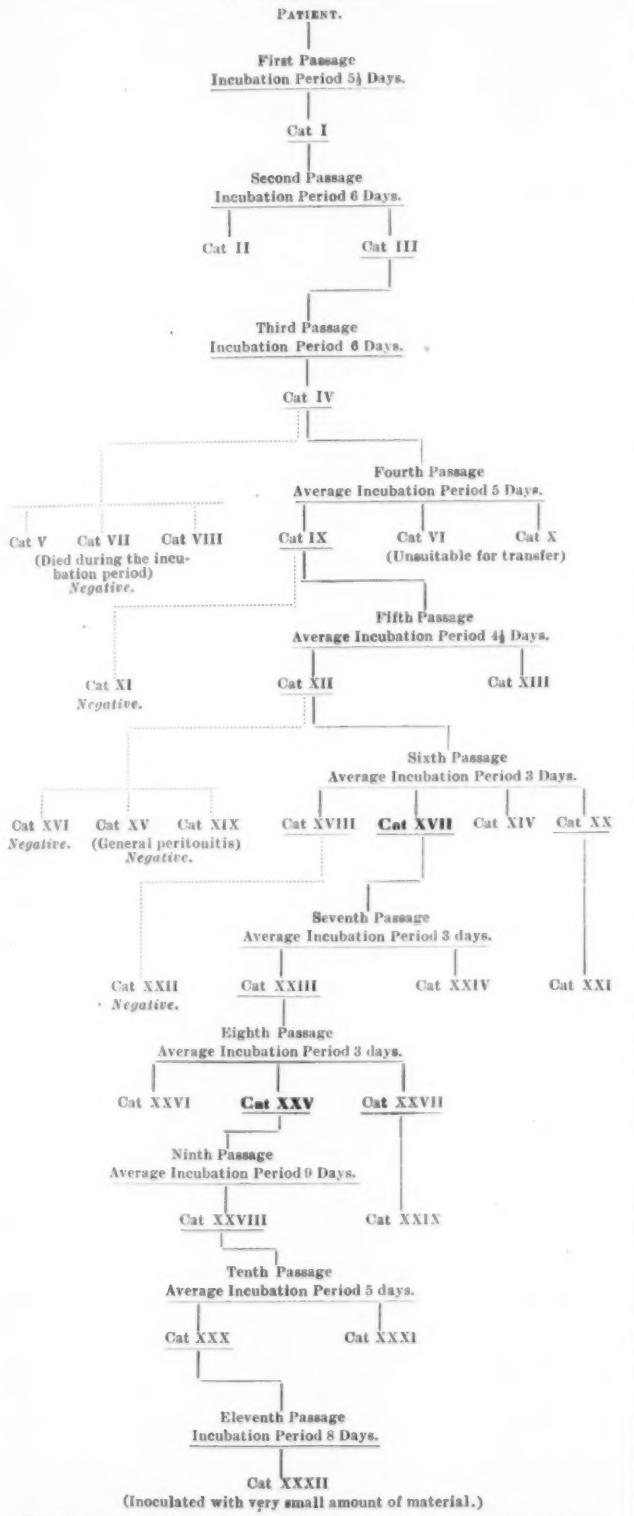


Diagram 1.

This diagram includes the average incubation period of all animals used in each generation except two adult cats. These were not included because adults are known to be unfavorable subjects with longer incubation periods and do not offer fair comparison with the incubation period of younger and more susceptible animals which were used in the other inoculations.

There were two conditions which were especially difficult to control; namely, (1) bacterial infection, and (2) in a few animals, the failure of the amœbæ to infect even under optimum conditions. The accompanying diagram (No. II) shows the total number of animals used in the individual passages with the general result in each case. Table I gives the details of the animals which became infected and Table II those which did not become infected. More complete protocols are given at the end of the paper

DIAGRAM II, SHOWING THE NUMBER OF ANIMALS USED AND THE GENERAL RESULTS.



The eight animals which failed to contract dysentery are grouped on the left and are connected by the broken line.

TABLE I.

DETAILS OF ANIMALS WHICH BECAME INFECTED.

No. of passage.	Size of cat.	Method of inoculation.	Incubation period.	Remarks.
1st passage.	½ grown.	Intracæcal injection.	5-6 days.	Killed after 9 days.
2d "	½ "	" "	6 "	Died after 44 days.
2d "	½ "	" "	6 "	Died after 31 days. Blood culture +.
3d "	½ "	" "	6 "	Died after 10 days. Blood culture +.
4th "	½ "	" "	4 "	Died after 5 days. Blood culture +.
4th "	.....	Rectal tube injection.	6 "	Killed after 7 days. Blood culture +.
4th "	½ "	" "	7 "	Killed after 90 days.
5th "	½ "	Intracæcal injection.	5 "	Died after 9 days. Blood culture +.
5th "	½ "	Rectal tube injection.	4 "	Died after 5 days.
6th "	½ "	Intracæcal injection.	5 "	Died after 66 days.
6th "	½ "	Rectal tube injection.	3 "	Died after 27 days. Blood culture +.
6th "	½ "	" "	3 "	Died after 4 days. Blood culture +.
6th "	½ "	Intracæcal injection.	1 "	Died after 1 day.
7th "	½ "	Rectal tube injection.	3 "	Died after 3 days. Blood culture +.
7th "	½ "	" "	3 "	Killed after 4 days. Blood culture —.
7th "	Adult.	" "	15-20 "	Recovered.
8th "	½ grown.	" "	3 "	Died after 4 days.
8th "	½ "	" "	3 "	Died after 10 days.
8th "	½ "	" "	3 "	Died after 7 days. Blood culture +.
9th "	½ "	" "	9 "	Killed after 9 days. Blood culture +.
9th "	½ "	" "	16 "	Died after 27 days.
10th "	½ "	" "	8 "	Died after 8 days.
10th "	½ "	" "	20 "	Died after 22 days.
11th "	½ "	" "	8 "	Killed after 11 days.

TABLE II.

DETAILS OF ANIMALS WHICH DID NOT BECOME INFECTED.

No.	Size of cat.	Method of inoculation.	Time and cause of death.
Cat V.	½ grown.	Intracæcal injection.	4 days after injection. Sudden death; autopsy negative; blood culture +.
Cat VII.	Adult.	" "	7 days after injection. General peritonitis.
Cat VIII.	"	" "	7 days after injection. General peritonitis.
Cat XI.	"	" "	3 days after injection. General peritonitis.
Cat XV.	½ grown.	" "	4 days after injection. General peritonitis.
Cat XVI.	Young adult	Rectal tube injection.	No signs of infection. Died two months later from other causes.
Cat XIX.	¾ grown.	Intracæcal injection.	1 day after injection. General peritonitis.
Cat XXII.	½ "	Rectal tube injection.	25 days after injection; cause of death unknown. Autopsy negative.

Effect on the Bacteria.—The bacteria interfered seriously with the laparotomies. In many instances it was evident from the anatomical lesions that the bacteria did not gain access to the peritoneum through the puncture wound of the syringe needle in the cæcum, but that they were able to penetrate the intestinal wall directly. Frequently the serous coat of the intestine was intensely inflamed for a distance of several inches. This inflammation occurred sometimes in the large intestine, but often in the small intestine and bore no definite relation to the puncture wound. There was always an accompanying general peritonitis and also a septicæmia. Moreover, these complications did not occur only in those animals in which a laparotomy was performed; the injection per rectum

of some of the animals resulted in a general septicæmia. Frequently this septicæmia was fatal before the incubation period of the entamœbæ had expired. This behavior was rare, however. In the majority of animals no septicæmia occurred until after the development of lesions in the intestine. In no case, however, did an animal die of an uncomplicated amœbic infection, but in all fatal cases there was a secondary septicæmia. This invasion was not only secondary, as a rule, to the amœbic infection, but it often came on very late; the blood culture was sterile in one instance only when taken in an advanced stage of the dysentery. The bacteræmia, therefore, though a secondary factor, is important in its bearing upon the cause of death in this series of animals.

It was also noted repeatedly that the development of septicæmia, or of extensive peritonitis, resulted in a failure of the entamœbæ to cause infection. This is mentioned on account of its direct bearing upon the possible explanation of the loss of the strain reported by Wenyon. In one of his animals the protocol records the development, not only of septicæmia, but of pyæmia. We have, therefore, in this strain reported by Wenyon and in the two strains reported in this paper, examples of the frequency and importance of the secondary invasion by bacteria. The records of the strains propagated by Werner and Darling do not give any information in regard to the influence of the accompanying bacteria.

On account of the importance of this secondary invasion, the various bacteria obtained at blood culture were studied to determine whether one or several species were carried over into the blood in any given individual and whether a single strain was carried through all the animals or whether several species were involved. An examination of all the cultures, except two, from the second to the ninth passage, inclusive, showed a pure culture of a single organism. This was a small streptococcus forming short chains and producing identical culture reactions on ordinary media. In one animal of both the third and fourth passages, the cultures contained a bacillus in addition to the usual streptococcus.

As regards the second source of difficulty it has been an almost universal experience that not infrequently infection fails to take place even under the most favorable conditions. Thus, when a series of young kittens are inoculated with fresh blood and mucus rich in trophozoites and cysts, a certain number of them will frequently escape infection. The explanation of this has not been investigated rigidly, but it is apparently due to a variety of self-evident accidental circumstances rather than to a natural insusceptibility of these individuals.

Relation to the General Laws Governing Infectious Processes.—This strain of entamœbæ, instead of constituting an exception, conforms to the general laws governing infectious processes. It serves to illustrate very well certain features of infectious diseases which are especially characteristic of the protozoa. The onset of the disease was acute. The course terminated fatally in the first attack or became chronic. It did not run an acute self-limited course, ending in death or complete recovery, such as occurs in some bacterial diseases and certain conditions of unknown etiology; *e. g.*, Asiatic cholera and yellow fever. There was no evidence from the clinical symptoms that one attack of dysentery conferred any immunity. When the condition of a carrier was developed, the infected individual did not enjoy freedom from symptoms, but was subject to acute relapses. As with many bacterial and protozoan parasites, the rapid passage of this strain through a series of individuals produced an increase in its virulence. The original incubation period of six days, which was required for the production of bloody mucous stools containing motile amœbæ, was shortened to two and three-fourths days by five passages. The total course of the disease from the time of inoculation was shortened in this instance to four days. This shortening was due, in part, to the early development of bacteræmia and an increase in the virulence of the accompanying bacteria. There was nothing which suggested in any way that the early appearance of amœbæ in the bloody mucous discharges could be connected with changes in the bacterial flora of the intestine. It is to be assumed that the exact details of behavior would vary with the individual strain. Thus, if a less virulent strain from a chronic case were injected into adult animals, there would surely be a smaller percentage of infections with less severe symptoms, and some strains might be comparatively difficult to propagate. Nevertheless, we feel that, under favorable conditions, the general rule will be that the passage of a strain will not be self-limited. Indeed, it would be of considerable interest, epidemiologically, if amœbic infection in susceptible animals died out after a few passages from one individual to another. If this were proved to be true, then amœbic dysentery, upon introduction in a susceptible species in an uninfected zone, would almost necessarily die out of itself, instead of becoming endemic.

Correlation with Previous Results.—The increase in virulence in this strain after a comparatively short number of passages does not exclude the possibility that a long continued passage through a great many animals might attenuate the virulence, as sometimes happens in the case of trypanosomes for example. The conclusion, however, is definitely refuted in this instance, that the entire strain necessarily undergoes morphological degenerations in that the virulence is lost, and that a strain dies out after at most from four to six passages. The question arises as to whether this strain constitutes an exceptional case or whether it represents the typical behavior of the pathogenic entamœbæ. An examination of the conditions governing the infection suggests that it is possible to correlate these apparently contradictory results. The conclusion that the passage of dysentery is self-limited is based upon two considerations; namely, that the parasites lose their virulence since the animals fail to become infected, and that the morphology of the amœbæ shows degenerative changes. In regard to the failure to infect, it must be remembered that several explanations as well as loss of virulence suggest themselves. In the first place the infection by feeding or by inoculation per rectum is extremely uncertain. The most unfavorable results are reported by Walker,[8] in Manila; with optimum infective material, no symptoms and no parasitization occurred

in thirteen animals representing three species. The uncertainty of feeding experiments and of injections per rectum as compared with the direct injection through the wall of the cæcum may account for some of the failures.

The effect of the bacteria which happen to accompany the entamœbæ is striking. In both of the strains reported in this paper and in that reported by Wenyon it has proven a troublesome factor. An examination of diagram No. II will show how easily this strain might have been lost purely through the effect of the accompanying bacteria. In two instances at crucial stages, its passage depended on the results in a single animal, although considerable precaution had been taken to secure a number of infected animals. It is not improbable that the selection of material at the onset of symptoms is advantageous both on account of the large numbers of active amœbæ that are obtained and also because the bacteria are somewhat less abundant.

In regard to the morphological changes which have been emphasized particularly by Darling, it is noteworthy that these also depend, in part, upon whether the entamœbæ are studied at the onset of symptoms or late in the course of the disease after the infection has become subacute or chronic. It is quite possible that long continued growth in one host with the possibility of specific reaction on the part of the host may produce changes in the infecting organisms, whereas the rapid passage from one susceptible animal to another might not afford any opportunity for the development of such changes. Thus, in some animals in our series the entamœbæ were perfectly typical at the onset of symptoms, but as the disease became chronic the entamœbæ became smaller in size, fewer in numbers, and less actively amœboid. Moreover, in the examination of the specimens it frequently happened that stools, though they were obtained perfectly fresh, contained small degenerating forms. It was evident that this was due to the retention of the stool in the lumen of the bowel under conditions which were not favorable to the growth or preservation of the amœbæ; on examining freshly obtained washings or on sacrificing such animals typical active organisms could usually be secured. Thus, there are many conditions arising in an animal which may result in the production of degenerative forms of entamœbæ. It must be emphasized that the occurrence of degenerative forms does not exclude the presence of perfectly typical forms at the site of the active lesions. Naturally, the sacrifice of an animal and an autopsy may be necessary to demonstrate the presence of typical organisms. When these degenerations do appear they may be the result of accidental complications in distinction to the explanation offered by Hartmann that the natural insusceptibility of cats sets up degenerative changes in the entamœbæ.

From these considerations we feel that there is not sufficient evidence to support the view that the passage of amœbic dysentery in animals is self-limited. The following factors must be taken into account in considering the explanation of the results that are reported in the literature:

1. Some of the strains may have been lost on account of the virulence of the accompanying bacteria.

2. The virulence of the entamœbæ may have been lost by re-inoculating late in the course of the infection of a given individual rather than at the first onset of symptoms.

3. Rectal injections of trophozoites have proven definitely less effective than direct inoculation through the wall of the cæcum into the lumen.

4. The degenerative changes in morphology which have been described can be explained in part by the nature of the material which was selected for examination.

In view of these considerations we feel definitely that the previous failures were due, like Wenyon's, to accident, and not to any inherent changes occurring in the entamœbæ as a result of the subinoculation.

SUMMARY.

1. Two strains of amœbic dysentery were investigated with the object of securing continuous propagation by subinoculation through a series of animals. The first strain was lost in the second passage by accident. The second strain was carried through eleven successive passages in kittens.

2. This strain increased in virulence and no degenerative changes appeared in the morphology of the entamœbæ obtained at the site of active lesions. The characteristics of the clinical course and pathological lesions were retained throughout the eleven passages.

3. The propagation proved to be considerably complicated by the virulence of the accompanying bacteria.

4. The successful propagation of one strain through eleven passages in animals, with an increase in virulence of the entamœbæ and a retention of the typical features of their morphology, is in conformity with the general laws of protozoan and bacterial infections.

DISCUSSION.

We consider that the general behavior of this strain of amœbic dysentery will prove to be typical of this species and that *Entamœba histolytica* will conform to the general rules of parasitology in regard to the subinoculation of a susceptible species of animals, especially with regard to the retention of virulence, through at least a moderate number of passages.

There is not sufficient evidence for the view which is generally expressed in the literature to the effect that the subinoculation of a strain of amœbic dysentery is definitely self-limited to a few passages. This self-limitation is ascribed to loss of virulence and changes in the morphology of the entamœbæ. Exactly the opposite result was obtained in the eleven passages which were secured with the strain reported in this paper. It is possible, however, to correlate these contradictory results. The following factors suggest themselves for consideration:

1. Some of the strains which were supposed to be self-limited may have been lost on account of the virulence of the accompanying bacteria.

2. The virulence of the entamœbæ may have been lost by re-inoculating late in the course of the infection of a given individual rather than at the first onset of symptoms.

3. Rectal injections of trophozoites have proven definitely less effective than direct inoculation through the wall of the cæcum into the lumen.

4. The degenerative changes in morphology of entamœbæ which have been described can be explained in part by the (a) long period which the specimens may have remained in the bowel before they were examined and by (b) the comparatively late stages of infection at which the specimens were selected. In view of these considerations, we feel that the previous failures were due to accident, and not to any inherent changes occurring in the entamœbæ upon subinoculation.

PROTOCOLS OF ANIMALS USED.

First Passage.

Oct. 6. Cat I. ¼ grown. Intracæcal injection with stools from patient. Oct. 11: Typical dysentery with many amœbæ. Oct. 15: Sick; continued bloody stools. Sacrificed: Gut normal except the rectum which was filled with bloody mucus; no gross ulceration present.

Second Passage.

Oct. 15. Cat II. ½ grown. Intracæcal injection from Cat V. Oct. 21: Typical dysentery with many amœbæ. From Oct. 21 to Nov. 7 stools soft, no mucus, blood or amœbæ. Nov. 7: Typical bloody mucous stools with many amœbæ. Nov. 29: Coma; death. Autopsy: Large intestine showed diffuse inflammation with many motile amœbæ. Large liver abscess.

Oct. 15. Cat III. ½ grown. Intracæcal injection from Cat V. Oct. 21: Bloody and mucous stool. Oct. 21 to Nov. 7: Stools soft; no mucus, blood nor amœbæ. Nov. 7: Bloody mucous stools with amœbæ. Nov. 16: Death. Autopsy: Slight subcutaneous infection. Circumscribed ulceration with blood in lower 2 inches of large intestine. Blood culture from heart positive.

Third Passage.

Oct. 21. Cat IV. ½ grown. Intracæcal injection from Cats II and III. Oct. 27: Typical dysenteric stools with many amœbæ; continued until death. Oct. 31: Died. Autopsy: Ulceration of lower end of colon with mucus and blood containing active amœbæ. Blood culture positive.

Fourth Passage.

Oct. 27. Cat V. ½ grown. Intracæcal injection from Cat IV. Nov. 1: Died suddenly. Autopsy: Entirely negative. Blood culture (heart) positive.

Oct. 27. Cat VI. ½ grown. Intracæcal injection from Cat IV. Oct. 31: Died. Autopsy: Negative except for few amœbæ found in stained preparation of rectal contents. Blood culture (heart) positive.

Oct. 28. Cat. VII. Adult. Intracæcal injection from Cat. IV. Nov. 5: Died. Autopsy: General peritonitis.

Oct. 31. Cat VIII. Intracæcal injection from Cat IV. Nov. 7: Died. Autopsy: General peritonitis.

Oct. 31. Cat IX. Rectal tube injection from Cat IV. Nov. 6: Typical dysentery with blood and mucous stools and many amœbæ. Nov. 7: Sacrificed. Autopsy: Lower colon and rectum filled with bloody mucus containing many amœbæ. Blood culture (heart) positive.

Oct. 31. Cat X. Rectal tube injection from Cat IV. Nov. 7: Blood and mucous stool. This cleared up and animal remained perfectly well until sacrificed in February. Feb. 2: Sacrificed. Autopsy: Entirely negative.

Fifth Passage.

Nov. 7. Cat XI. Adult. Intracæcal injection from Cat IX. Nov. 10: Sacrificed. General peritonitis.

Oct. 7. Cat XII. ¼ grown. Intracæcal injection from Cat IX. Nov. 12: Typical dysentery with blood, mucus and numerous amœbæ in stools; continued until death. Nov. 16: Died. Autopsy: Marked swelling, thickening and ulceration of lower 3 in. of large bowel. Contents consist of blood and mucus with innumerable amœbæ. Blood culture (heart) positive.

Nov. 7. Cat XIII. ½ grown. Rectal tube injection from Cat IX. Nov. 11: Typical dysentery with many amœbæ. Nov. 12: Died. Autopsy: No gross lesions in bowel. Contents consisted of blood and mucus with many amœbæ.

Sixth Passage.

Nov. 12. Cat XIV. ½ grown. Intracæcal injection from Cat XII. Nov. 17: Typical stools with few amœbæ. No further symptoms noted. Jan. 18: Died. No autopsy.

Nov. 12. Cat XV. ½ grown. Intracæcal injection from Cat XII. Nov. 16: Died. Autopsy: Extensive subcutaneous abscess: general peritonitis.

Nov. 12. Cat XVI. ¾ grown. Rectal tube injection from Cat XII. Similar injection repeated on Nov. 13. No symptoms noted, no amœbæ found. Died in January. Autopsy negative.

Nov. 16. Cat XVII. ½ grown. Rectal tube injection from Cat XII. Nov. 19: Typical dysenteric stools with many amœbæ; continued until Nov. 25. Dec. 12: Autopsy: Colon negative; purulent pericarditis and empyema.

Nov. 16. Cat XVIII. ¼ grown. Rectal tube injection from Cat XII. Nov. 19: Typical dysentery with many amœbæ. Nov. 20: Died. Autopsy: Thickening and ulceration in rectum. Blood culture (heart) positive.

Nov. 16. Cat XIX. ½ grown. Intracæcal injection from Cat XII. Nov. 17: Died. Autopsy: General peritonitis.

Nov. 16. Cat XX. ¼ grown. Intracæcal injection from Cat XII. Nov. 17: Died. Autopsy: General peritonitis; colon contains mucus and slight amount of blood with many amœbæ.

Seventh Passage.

Nov. 17. Cat XXI. ⅛ grown. Rectal tube injection from Cat XX. Nov. 20: Typical dysentery with amœbæ. Died in late afternoon. Autopsy negative. Blood culture positive.

Nov. 19. Cat XXII. ⅛ grown. Rectal tube injection from Cat XVIII. Dec. 8: No dysentery nor amœbæ. Died. Autopsy negative.

Nov. 19. Cat XXIII. ⅛ grown. Rectal tube injection from Cat XVII. Nov. 22: Typical dysentery with many amœbæ. Nov. 23: Killed. Superficial ulceration over rectal mucosa with many amœbæ. Blood culture negative.

Nov. 19. Cat XXIV. Adult. Rectal tube injection from Cat XVII. Dec. 8: Typical dysentery with many amœbæ. Jan. 14: Died. Autopsy negative.

Eighth Passage.

Nov. 23. Cat XXV. ⅛ grown. Rectal tube injection from Cat XXIII. Nov. 26: Typical dysentery with active amœbæ. Amœbæ very large size. Nov. 27: Died. Autopsy: Rectal ampulla injected and filled with bloody mucus containing many amœbæ.

Nov. 23. Cat XXVI. ⅛ grown. Rectal tube injection from Cat XXIII. Nov. 26: Dysentery with amœbæ. Dec. 2: Died. Autopsy: Rectum hyperæmic with ulceration. Contents showed very numerous amœbæ.

Nov. 23. Cat XXVII. ¼ grown. Rectal tube injection from Cat XXIII. Nov. 26: Animal is distinctly sick—no stool examination recorded. Dec. 1: Died. Autopsy: Marked injection with swollen granulomatous ulceration of mucosa in region of sigmoid and

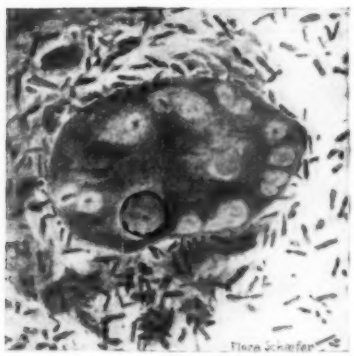


FIG. 1.

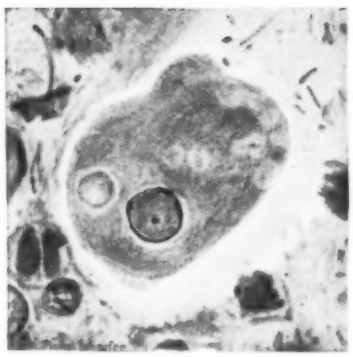


FIG. 2.

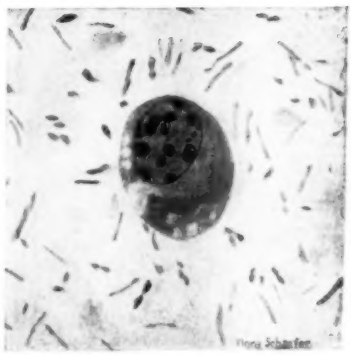


FIG. 3.

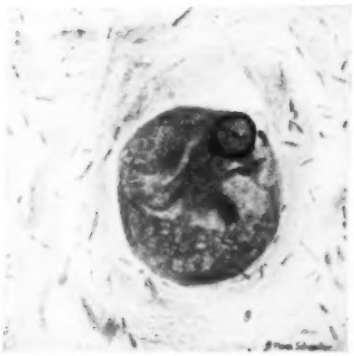


FIG. 4.

especially over the rectum. Contents showed many typical amœbæ. Blood culture positive.

NINTH PASSAGE.

Nov. 27. Cat XXVIII. ¼ grown. Rectal tube injection from Cat XXV. Dec. 6: Animal sick; stools contain numerous active amœbæ. Sacrificed. Colon contents in cæcal region contained much pus and active amœbæ. Mucosa of rectum injected and swollen, no ulceration; contents here contain blood and mucus with numerous amœbæ. Blood cultures positive.

Dec. 1. Cat XXIX. ¾ grown. Rectal tube injection from Cat XXVII. Dec. 16: Bloody stools. Dec. 26: Distinctly sick; numerous bloody stools. Dec. 28: Died. Autopsy: Slight hyperæmia of rectal mucosa; contents of bowel here are bloody. No microscopic examination for amœbæ noted.

TENTH PASSAGE.

Dec. 6. Cat XXX. ¼ grown. Rectal tube injection from Cat XXVIII. Dec. 14: Found dead. Autopsy: Colon hyperæmic with swollen granulomatous appearance over rectal mucosa. Numerous dead amœbæ.

Dec. 6. Cat XXXI. ¼ grown. Rectal tube injection from Cat XXVIII. Dec. 26: Typical dysenteric stools. Dec. 28: Died. Autopsy: Slight hyperæmia of rectum; no ulceration.

ELEVENTH PASSAGE.

Dec. 11. Cat XXXII. ⅛ grown. Rectal tube injection from Cat XXX. Dec. 19: Dysenteric stools containing many amœbæ. Dec. 22: Typical stools containing many amœbæ. Sacrificed. Autopsy: Hyperæmia and swelling of rectal mucosa. Contents of gut at this point showed mucus and blood with many typical and actively motile amœbæ.

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EXPLANATION OF TROPHOZOITES IN PLATE.

(Magnification, × 1500.)

FIG. 1.—From the stool of the patient.

FIG. 2.—From the eleventh passage in animals.

FIGS. 3 and 4.—Degenerating forms from the second passage from a fresh stool, obtained on the third day after the onset of symptoms.

THE BLOOD-PICTURE IN HODGKIN'S DISEASE.[1]

SECOND PAPER.

By C. H. BUNTING, M. D.

(*From the Pathological Laboratory of the University of Wisconsin.*)

In an earlier paper[2] on Hodgkin's disease, I pointed out characteristics in the blood-picture which seemed at that time to warrant the conclusion that the diagnosis of the disease might be made from blood smears with a considerable degree of accuracy. The earlier paper was based on a study of 11 cases, in all but one of which the diagnosis was established by microscopical examination of a test-gland; and in the one exception, the clinical picture and the course of the disease left no doubt as to the diagnosis.

During the past year it has been possible, through the courtesy of friends in the medical profession, to study the blood of 14 additional cases, in which the diagnosis has been established by the histological examination of a test gland. It has thus been possible to confirm and strengthen the earlier findings.

The series of cases studied includes 15 males and 10 females, a somewhat higher percentage of the latter sex than is usually given. It is further rather striking, that the great majority of the males are under the thirty-third year, while the majority of the females are above that age.

The study of the blood in these cases has shown, as indicated by the tabulated results, that there is a deviation from the normal leukocytic picture in all cases, but that there is not a single constant picture found in them. Instead, it is possible to divide the cases into two distinct groups according to the differential count of the leukocytes. The first group, including cases of a year or less in duration, shows a normal or slightly increased total leukocyte count with a normal or decreased percentage of polymorphonuclear neutrophiles. The second group includes the cases of greater duration for the most part, and shows a sharp leukocytosis, running in one case (as far as could be determined from the smear ratio of 1 white cell to 29 red cells), to at least 100,000 leukocytes per cmm. This leukocytosis is accompanied by an increase of the neutrophiles to a percentage between 72 and 90—a percentage ordinarily considered of value in diagnosing a suppurative process in the body, yet occurring in Hodgkin's disease in the complete absence of pus formation.

The explanation of this change in blood-picture is not en-

[1] This work has been aided by a grant from the Rockefeller Institute of Medical Research, New York.

[2] Johns Hopkins Hosp. Bull., 1911, XXII, 369.

GROUP ONE.

Case No.	Sex.	Age.	Appar. duration.	Leukocyte count.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I	M.	21	4 mos.	7,500	51.2	3.2	1.6	25.4	10	.....	8.6
II	M.	10	1 yr.	9,500	56.2	8.6	5.4	16.4	7.4	.....	11
IV	F.	40	9 mos.	.....	36.	0.6	0.2	39.2	10.6	2.8	10.6
V	M.	8	5 mos.	9,000	59.4	4.6	0.4	21.8	3.6	.....	10.2
VII	F.	64	3 mos.	4,480	54.8	4.2	0.4	20	9.8	1.6	9.2
IX	M.	5	5 mos.	4,200	54.4	2.4	0.2	22.6	8.6	2.4	9.4
XIII	M.	31	14 mos.	6,000	44.8	4.6	0.4	19.4	13.4	2.4	15.0
XVIII	M.	33	6 mos.	.....	64.2	0.4	0.0	16.4	9.2	0.6	9.2
XIX	M.	33	5 mos.	.....	46.8	0.6	1.4	33.4	3.8	0.4	13.6
XXI	M.	37	18 mos.	low	70.4*	1.8	0.4	10.6	3.6	0.0	13.2
XXIII	M.	17	?	10,000	60.4	2	0.6	20.8	6.2	0.2	9.8

* Count taken with recent surgical incision still unhealed.

GROUP TWO.

III	M.	30	*	10,000	79.4	0.2	0.4	5.8	.....	3.4	10.8
VI	M.	16	?	18,000	81.6	0.6	0.4	4.2	3.	1.6	8.6
VIII	M.	33	.....	.....	76.2	1.4	0.6	7.6	.....	6.	8.2
X	M.	.....	.....	14,300	84.	0.0	0.0	3.8	1.0	1.0	10.2
XI	M.	22	1 yr.	.....	81.8	0.2	0.6	2.6	2.6	1.0	11.2
XII	F.	33	1 yr.	19,000	85.4	2.8	0.0	3.2	0.4	0.2	8.
XIV	F.	52	2 yrs.	100,000	89.2	0.0	0.0	2.4	1.0	0.6	4.
XV	F.	20	1 yr.	9,000	84.4	1.2	0.0	2.2	4.2	0.4	7.6
XVI	F.	34	†	12,400	85.8	0.2	0.4	4.4	3.2	0.6	5.4
XVII	F.	38	2 yrs.	22,000	82.6	2.	0.0	5.2	2.4	0.0	7.8
XV	F.	24	1 yr.	20,000	90.4	0.4	0.0	2.4	1.4	0.0	5.4
XXII	F.	22	2 yrs.	6,200	78.	2.6	1.2	4.4	0.2	0.0	13.6
XXIV	M.	27	7 mos.	44,000	84.	1.6	0.0	8.8	0.4	0.2	5.
XXV‡	F.	17	4 mos.	12,000	72.6	0.9	0.4	15.3	3.0	0.4	7.4

* Over 1 year. † 10 months. (?)

N. = Neutrophile, E. = Eosinophile, B. = Basophile, S. L. = Small Lymphocyte, L. L. = Large Lymphocyte, L. M. = Large Mononuclear, Tr. = Transitional.

‡ Case XXV was apparently counted in a transition from the early to the late blood-picture. Later counts show an increase in neutrophiles to 78.4% and a decrease in lymphocytes to 7.6%.

tirely clear. While the primary blood-picture is usually found in cases of relatively short duration, and with comparatively localized lesions, there are enough exceptions in the series to indicate that these are not the sole factors. If it were possible to examine every gland in every case one might find a pathological explanation for the change. Glands from two of the cases with the sharpest leukocytosis indicated that in these the disease was progressing more intensely. There was more necrosis and a marked infiltration of the gland and surrounding tissue with neutrophile leukocytes. As a result of the bacteriological investigations of Dr. Yates and myself,[3] I was on the point of accepting the possibility that complicating infection with staphylococci might be responsible for this increased intensity of reaction when cultures from several glands in a very recent case with such a picture gave only the diphtheroid organism. Inoculation of monkeys with the diphtheroid organism has produced the primary blood-picture, with a slight tendency toward the secondary picture in one monkey, inoculated with an organism of increased virulence. Pathological study of these experimental lesions indicates strongly that while necrosis of lymphocytes leads to chemotaxis for eosinophiles, the necrosis of the proliferated endothelioid cells and fibroblasts leads to positive chemotaxis for neutrophiles. Thus, in the cases with greater intensity of the process, we have the neutrophile leukocytosis.

Turning to the other changes in the differential count, the most striking feature, as indicated in the earlier paper, is the increase in the so-called transitional leukocyte—the large mononuclear cell with indented or lobed nucleus, abundant protoplasm and fine azurophile granulation with Wright's stain. These cells are absolutely increased in all cases, and relatively increased in all except those with well marked leukocytosis; and even in these latter cases the transitionals are the most numerous cells except the neutrophiles. Thus, in the group of cases with the primary picture, one finds the percentage varying from 8.6 to 15, as opposed to a normal of 7.5; while in the secondary group, the percentage is above normal excepting in four cases with a relatively sharp leukocytosis, and in these it varies from 4 to 5.4. There seems every evidence from blood counts and gland sections in a variety of conditions that these cells are derived from the cells of the germinal centers of lymphoid tissue, and from cells lying upon the reticulum of the lymph cords, and not from the endothelial lining of the lymph sinuses.

The lymphocytes, except for a moderate increase during the first few months of the disease (35.4, 37.2, 49.8 per cent), show a gradual percentage diminution, until in the later cases they vary from 7.6 to 3.4. Apparently the toxin active in the disease, in small doses, leads to a stimulation of lymphocyte production, but in large doses leads to their destruction.

The circulating eosinophile cells show quite a variation in number in the different cases. This seems to depend chiefly upon the reactive power of the marrow. The chemotactic substance which attracts the eosinophile to the glands appears to be some product resulting from the destruction of lymphocytes. Even in the early phase, when this destruction is relatively slight, and there is chiefly proliferation of lymphocytes, the normal marrow does not seem able to compensate and there is a circulatory deficiency. Later, in the well established cases, even with greater demands, marrow compensation is usually excessive, and there is a moderate eosinophilia. In exceptional cases there may be an extreme eosinophilia as shown by a blood smear sent me from the medical laboratory of the Johns Hopkins Hospital, in which there was 68 per cent of eosinophiles in a count of 20,000, and as seen in Case XII of this series, in whom on one occasion there was 33 per cent of eosinophiles in a count of 30,000 leukocytes. In the latter case a rather marked skin reaction to the X-ray may have accounted for the increase.

The basophiles are increased in very early cases, but later almost disappear from the circulation. Basophiles, as well as eosinophiles, may be found in smears from the lymph glands in Hodgkin's disease. This, taken with the blood counts in monkeys inoculated with the diphtheroid organism, suggests that the basophile reaction is specific. However, basophiles appear to be constantly increased in chronic nasopharyngeal and nasal sinus infections, and it may be that such infections in conjunction with the primary lesion of the disease, lead to the early increase in Hodgkin's disease.

In all cases the great increase in blood platelets, noted in the earlier paper, has been found, and with the increase there are always abnormally large platelet masses and pseudopodia.

One may summarize the blood finding then as follows: throughout the disease there are two constant features, an

[3] Arch. Int. Med., 1913, XII, 236.

increase in blood platelets and an absolute increase in the transitional leukocytes. In regard to the other elements, in early cases there is a transitory increase in lymphocytes and basophiles, and a deficiency in eosinophiles, with a normal or low neutrophile count, followed by a gradual decrease in lymphocytes and a moderate eosinophilia. In late cases there is a marked neutrophile leukocytosis, and a diminution in percentage of all other elements except the transitional leukocyte.

All of these features of the blood picture in Hodgkin's disease have been reproduced in the monkey following inoculation with the diphtheroid organism isolated from cases of the disease. One finds, as shown by the counts from one monkey here given, the prompt increase in the transitionals and basophiles, the early deficiency in eosinophiles followed by an eosinophilia, and the early stimulation of the lymphocytes, followed by a gradual reduction. The counts are as follows:

Date.	Total count.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
April 15	22,300	51.0	2.4	0.2	40.8	2.8	0.4	2.4
19	Inoculation							
21	17,600	45.4	1.0	0.8	38.2	5.2	0.6	5.8
24	14,000	28.2	1.6	1.2	56.0	5.2	0.6	7.2
May 1	31,250	62.0	1.8	0.4	27.2	2.2	0.4	6.0
23	20,000	42.8	2.2	0.8	46.0	2.2	1.0	5.0
24	Inoculation							
28	.....	34.4	5.0	0.0	49.6	1.8	0.4	8.8
June 7	Inoculation							
11	14,000	29.8	5.4	0.2	54.8	4.6	5.2	7.0
21	Inoculation							
30	.....	50.0	1.8	0.0	38.0	2.0	0.2	8.0
30	Inoculation							
July 1	.....	51.8	2.2	0.2	37.2	2.0	0.2	6.4
2	.....	48.6	3.8	0.2	36.2	3.6	0.4	7.2
3	.....	51.2	1.6	0.2	35.	3.2	0.2	8.6
5	24,000	52.8	2.4	0.0	32.	4.6	0.4	7.8

A gland, removed after the last count recorded, showed many mitoses in endothelioid cells, apparently accounting for the circulatory increase in transitionals. There was also well-marked eosinophilic infiltration, and a lessened production of lymphocytes.

From the foregoing it may be seen that there are sharply marked blood changes in Hodgkin's disease. The question naturally arises: are they of value in diagnosis of doubtful cases? It is my belief that given a case with chronic glandular enlargement and without any suppurative process, and the blood picture which I have designated as the late or secondary, the diagnosis is established. Given the chronic glandular enlargement and the primary blood picture, diagnosis is somewhat more difficult, but, in my experience, can in the great majority of cases be made with certainty. The diagnosis usually lies between Hodgkin's disease and tuberculosis. There are apparently two distinct pictures in tuberculosis of the glands—that found before there is any softening and abscess formation in the glands, and that found when such a change has occurred. The primary picture here is quite distinctive; the secondary picture is more like the early Hodgkin's picture, but the clinical examination in such a case would determine the abscess formation.

The blood counts which I have made in cases of tuberculosis of the glands are as follows:

CASES WITHOUT ABSCESS FORMATION.

Cases.	Total count.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
I	.....	56.	1.8	0.2	26.4	5.	3.	7.6
II	.....	61.8	1.8	0.2	19.4	6.	1.	6.4
III	7,200	59.8	0.2	0.2	31.	1.4	0.0	7.4
IV	10,000	58.	0.6	0.2	33.	2.2	0.0	6.0
V	.....	61.2	0.6	0.2	28.6	1.8	0.8	6.0
VI	5,000	46.4	1.4	0.2	45.2	1.4	0.0	5.4
VII	.....	61.6	1.2	0.2	20.2	9.	0.6	7.2
VIII	9,400	57.6	1.2	0.6	28.	7.4	0.4	4.8

CASES WITH ABSCESS FORMATION.

I	9,000	41.6	2.4	0.0	43.2	4.4	0.4	8.
II	.....	63.	1.2	0.6	19.	6.	2.2	8.
III	11,000	68.6	3.6	0.2	12.4	6.6	0.6	7.6
IV	....	33.4	4.2	0.6	20.	7.6	0.2	8.
V	10,800	64.6	5.4	0.2	21.6	0.8	0.8	6.6

The quite constant low eosinophile count associated with a low transitional count in the primary group of tuberculosis cases is in definite contrast to the picture in Hodgkin's disease. In addition, while platelets are usually increased in tuberculosis, one seldom finds so great an increase as in Hodgkin's disease, and the abnormally large platelet masses are, in my experience, lacking in the tuberculosis picture. With the exercise of judgment, therefore, the diagnosis may be made from the blood smear.

One case has thrown some doubt on the possibility of diagnosing between Hodgkin's disease and some forms of the so-called malignant lymphomata. In this case, with a primary orbital tumor of slight greenish cast, and general glandular and splenic enlargement, the blood-picture could not be distinguished from that of Hodgkin's disease. Two counts in that case made at an interval of nine months are as follows:

N.	E.	B.	S.L.	L.L.	L.M.	Tr.
54.6	0.9	0.9	23.3	8.2	0.4	11.5
61.4	0.4	0.8	20.6	3.2	0.4	13.2

This finding may not invalidate the blood picture in Hodgkin's disease. It may, when taken with the fact that there was isolated from this case an organism similar to, if not identical with, that obtained constantly in Hodgkin's disease, explain the difficulty of morphologists in drawing a sharp line between the various forms of apparently malignant glandular hyperplasia.

Abstracts of the Hodgkin's disease cases, upon which this report is based, follow:

CASE I (Dr. Yates).—November 20, 1908. Male, white, 21. Onset of disease, July, 1908. Cervical and axillary glands involved. Test gland removed October 30, 1908, showed early Hodgkin's changes. Gradual improvement under treatment. Clinically well since June, 1909, except for some nasal infection.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.		L.M.	Tr.
XI. 20, '08.....	5,304,000	7,500	51.2	3.2	1.6	25.4		10.		8.6
III. 4, '09.....	4,968,000	4,800	55.2	2.4	0.8	23.6		6.6		11.4
VI. 11, '09.....	5,600,000	7,000	65.8	2.8	0.0	16.8	7.6		1.2	5.8
II. 16, '10.....	5,800,000	7,000	59.8	4.0	1.4	15.4	8.8		1.8	8.8
VI. 9, '11.....	.....	8,500	65.0	2.6	1.2	21.2	3.		0.6	6.4
IV. 17, '12.....	.....	5,000	42.2	5.8	0.6	41.4	1.8		0.4	7.8
XI. 17, '13.....	.....	10,000	60.	2.6	0.8	27.4	3.8		0.2	5.2

CASE II (Dr. Yates).—Male, white, 10. Large mass of discrete glands in left cervical region of at least one year's duration previous to removal, November 10, 1908. Glands show well-marked Hodgkin's picture. Von Pirquet reaction negative October 8, 1910.

Gradual improvement under treatment. Increase in size of one gland left at first operation in March, 1913. Removed. Apparently well—1914.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.		L.M.	Tr.
IV. 1, '09.....	4,712,000	9,500	56.2	8.6	0.4	16.4		7.4		11.0
I. 22, '10.....	5,250,000	9,600	63.6	3.6.	0.0	12.0	12.0		2.0	6.8
III. 12, '10.....	.....	.....	53.4	5.2	1.0	13.	16.		1.6	9.8
X. 8, '10.....	4,980,000	9,800	53.2	5.2	0.4	27.8	4.		1.4	8.0
II. 13, '12... .	.....	8,000	57.	4.4	0.2	27.4	4.		0.2	6.8
VI. 3, '12.....	5,300,000	7,000	64.	4.	0.2	19.8	3.2		0.2	8.4
III. 10, '13.....	.....	.....	39.6	10.4	0.6	25.	10.4		1.0	13.0
IX. 18, '13.....	.....	.....	64.2	3.6	0.6	22.	1.8		0.0	7.8

NOTE.—Recurrence found after paper was in press, associated with return of blood picture to that noted earlier during active stage of the disease.

CASE III.—April 1, 1909. Male, white, 30. Seen 2 weeks after second operation for glands of neck. First operation 6 months previous at Rochester. Diagnosis, Hodgkin's disease.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.		L.M.	Tr.
IV. 1, '09.....	4,560,000	10,000	79.4	0.2	0.4	5.8		3.4		10.8

CASE IV (Dr. Tupper, Eau Claire, Wis.).—February 5, 1910. Female, white, 40. Onset, — months previous in right inguinal glands. Subsequent involvement of left inguinal, left axillary, left and right cervical glands. Test gland shows well-marked active Hodgkin's picture. Death in October, 1910.

BLOOD COUNTS.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 5, '10.....	36.	0.6	0.2	39.2	10.6	2.8	10.6

CASE V (Dr. Yates).—November 9, 1909. Male, white, 8 years. Enlargement of cervical glands began 5 months previous to date. Left inguinal glands also enlarged. Test gland, November 30, 1909, shows hyperplastic stage of lesion. January, 1910, cervical glands removed. October, 1910, von Pirquet test negative. April, 1911, mucous membrane hæmorrhages, anæmia. Died January 10, 1912. Involvement of mesenteric glands, chylous ascites, wasting.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.		L.M.	Tr.
XI. 9, '09.....	.....	9,900	59.4	4.6	0.4	21.8		3.6		10.2
XI. 30, '09.....	.....	.....	50.8	5.8	0.6	26.8		7.2		8.8
II. 26, '10.....	5,000,000	5,000	55.2	1.4	0.4	22.4	9.2		2.0	9.4
IX. 7, '10.....	5,160,000	8,700	59.4	1.	1.2	16.4	6.6		5.	10.4
IV. 21, '11.....	3,456,000	4,800	63.2	1.8	1.	10.2	4.6		1.4	17.8
Transfused.										
IV. 24, '11.....	3,176,000	3,800	54.	6.8	0.2	17.8	4.8		1.8	14.6
V. 2, '12.....	2,624,000	8,300	67.6	1.4	1.4	6.8	9.6		0.6	12.6
Transfused.										
V. 5, '11.....	2,760,000	4,500	54.6	2.6	2.	18.8	7.6		0.6	13.8
V. 9, '11.....	3,200,000	4,000	50.8	4.	1.6	25.8	6.4		0.6	10.8
Transfused.										
V. 10, '11.....	.....	.....	60.	9.8	0.6	8.2	6.8		0.4	14.2
V. 13, '11.....	3,400,000	3,500	56.2	4.8	0.8	17.6	6.4		0.4	13.8
V. 22, '11.....	3,712,000	3,400	55.8	3.2	0.0	19.8	3.6		1.2	16.4
V. 29, '11.....	3,680,000	3,600	56.4	3.4	1.6	18.	8.1		0.6	11.8

CASE VI (Dr. Sullivan, Madison, Wis.).—March 1, 1910. Male, white, 16. Left cervical glands much enlarged. Marked induration of neck. Enlargement noted for only 1 month, but the amount of sclerosis in test gland suggests greater duration. March 10, wound resulting from removal of gland for diagnosis still unhealed. May 13, wound healed but induration of neck marked. Death during 1911.

BLOOD COUNTS.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
III. 10, '10.....	18,000	81.6	0.6	0.4	4.2	3.	1.6	8.6
V. 13, '10.....	27,000	80.6	1.6	0.0	7.8	2.8	0.8	6.4

CASE VII (Dr. Bennett, Oregon, Wis.).—January 5, 1910. Female, white, 64. In October, 1909, general glandular enlargement with clinical diagnosis of Hodgkin's disease. Death June 30, 1910.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
X. 24, '09.....	3,200,000	4,480							
I. 5, '10.....	.....	.....	54.8	4.2	0.4	20.0	9.8	1.6	9.2

CASE VIII (Dr. Yates).—Male, white, 33. Onset in March, 1907, with supraclavicular glandular enlargement. In September, 1908, supraclavicular and left axillary glands most enlarged. Some enlargement of right cervical, axillary and inguinal glands. October 30, 1908, excised gland shows typical and advanced Hodgkin's disease. Death occurred May 20, 1909.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.		L.M.	Tr.
I. 10, '09.....	76.2	1.4	0.6	7.6		6.0		8.2

CASE IX (Dr. Yates).—October 3, 1910. Male, white, 5. Marked enlargement of left cervical glands of 5 months duration. Test gland shows well marked Hodgkin's changes. Death from shock at operation.

BLOOD COUNT.

Date.	R. b. c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
X. 3, '10.....	5,160,000	4,200	54.4	2.4	0.2	22.6	8.6	2.4	9.4

CASE X (Dr. Yates).—Male, white, cervical Hodgkin's. Count made 2 months previous to death of patient.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 30, '10.....	14,300	84.	0.0	0.0	3.8	1.0	1.0	10.2

CASE XI (Dr. Baird, Eau Claire, Wis.).—December 8, 1910. Male, white, 22. Enlargement of supraclavicular gland noted one year previous. Axillary glands enlarged at date. Test gland shows definite Hodgkin's picture.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 8, '10.....	81.8	0.2	0.6	2.6	2.6	1.	11.2

CASE XII (Dr. Yates).—Female, white, 33. October, 1911. Enlargement of the right cervical and axillary glands of one year's duration. Test gland showed a picture of advanced typical Hodgkin's disease. Cervical glands removed February 13, 1912. Subsequent X-ray treatment. Removal of recurrences in right axilla and left sub-clavicular region January, 1913; March, 1913; July, 1913. Clinically well 1914.

BLOOD COUNTS.

Date.	W. b. c.	N.	E.	B.	S. L.	L.L.	L. M.	Tr.
IX. 27, '11....	19,000	85.4	2.8	0.0	3.2	0.4	0.2	8.0
X. 3, '11....	21,000	72.4	11.0	0.2	5.6	2.2	0.2	8.4
X. 31, '11....		73.8	6.2	0.8	7.6	2.5	0.6	8.2
XII. 1, '11....	35,000	84.	2.9	1.1	4.7	0.9	0.1	6.3
XII. 29, '11....	21,000	72.	11.0	0.4	9.2	0.9	0.0	5.5
II. 13, '12....		74.2	9.2	0.2	9.2	1.2	0.0	6.0
III. 15, '12....	30,000	48.0	36.	1.4	9.0	1.2	0.0	4.4
IV. 10, '12 ..	17,000	73.2	10.	0.6	7.2	0.6	0.0	8.4
V. 3, '12....	17,000	74.2	9.6	0.2	10.8	1.4	0.0	3.6
VI. 1, '12....	12,500	77.8	7.4	0.8	8.8	0.0	0.2	6.0
X. 8, '12....	16,000	70.	12.6	0.0	8.6	1.8	0.2	7.0
XI. 27, '12....	15,000	72.6	8.6	0.4	7.4	3.4	0.0	7.6
I. 11, '13....	16,000	80.3	5.0	0.1	4.2	2.6	0.2	7.6
II. 14, '13....	13,000	71.8	12.2	1.0	7.4	1.4	0.0	6.2
III. 3, '13....	15,500	64.8	13.2	0.6	12.4	3.2	0.0	5.8
IV. 12, '13....	15,000	74.	6.8	1.0	10.0	0.8	0.0	7.4
VII. 14, '13....	15,000	71.	8.8	1.8	10.6	1.6	0.0	6.2
VIII. 4, '13....	7,000	51.0	10.0	0.0	27.0	0.8	0.2	11.0
I. 22, '14....	11,000	66.0	9.6	0.8	15.0	1.4	0.6	6.6

CASE XIII (Dr. L. F. Barker, Baltimore).—Male, white, 31. Enlargement of cervical glands, right side, of fourteen months duration. Test gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 23, '12.....	5,700,000	6,000	44.8	4.6	0.4	19.4	13.4	2.4	15.0

CASE XIV (Dr. S. T. Reeves, Albany, Wis.).—Female, white, 50. The glandular swelling had first appeared in the left cervical region two months previous to the patient's death. At the post mortem examination January 15, 1913, there was found rather general glandular involvement, but especial enlargement of the mesenteric and retroperitoneal nodes and of the lymphoid elements of the spleen. There was also a chylous ascites, well marked anemia and emaciation. Leukocyte count estimated from ratio of 1 white cell to 29 red cells.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 27, '12.....	100,000	89.2	0.0	0.0	2.4	1.0	0.6	4.0

CASE XV (Cook County Hospital, Chicago).—Female, white, 20. Marked enlargement of cervical glands; moderate of axillary and inguinal glands. Spleen palpable. Duration fourteen months. Test gland positive.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 18, '12.....	9,000	84.4	1.2	0.0	2.2	4.2	0.4	7.6

CASE XVI (Drs. Mayo, Rochester).—Female, white, 34. Four years previously she noticed a swelling on the right side of her neck, followed by the appearance of other small tumors. Ten months before date enlarged lymph-nodes appeared on the left side of the neck and in the right axilla. Six weeks previously nodes appeared in the left axilla. Physical examination revealed, in addition to these nodules, a mediastinal mass, and a six months' pregnancy, over which were felt discrete firm nodules which slipped under the examining hand. Test gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 9, '13.....	4,480,000	12,400	85.8	0.2	0.4	4.4	3.2	0.6	5.4

CASE XVII (Drs. Mayo, Rochester).—Female, white, 28. Marked enlargement of the cervical nodes and rather general glandular enlargement. The illness began with involvement of the cervical glands two years previous to date. Test gland showed extreme sclerosis with many giant cells and eosinophiles in the meshes.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 15, '13.....	22,000	82.6	2.0	0.0	5.2	2.4	0.0	7.8

CASE XVIII (Drs. Mayo, Rochester).—Male, white, 33. The patient had had an abscess of a tooth six months previously. About three weeks before coming to the hospital patient had noticed a painless swollen node in the left supraclavicular region. This had increased in size during the time of observation. The large node removed was of a uniform medullary appearance on gross section, and microscopically showed lymphoid and endothelial hyperplasia, with the presence of giant cells, beginning diffuse sclerosis and eosinophilic infiltration. The architecture of the node was destroyed.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 31, '13.....	64.2	0.4	0.0	16.4	9.2	0.6	9.2

CASE XIX (Dr. Frank Billings, Chicago).—Male, white, 32. Loss of weight since January 1, 1913. Glandular enlargement noted in February, 1913. On examination, in April, moderate enlargement of cervical, axillary and inguinal glands, tonsils and spleen. Abscess of right upper molar found. Gland showed early changes.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 28, '13.....	4,150,000	4,150							
V. 29, '13.....	.....	.....	46.8	0.6	1.4	33.4	3.8	0.4	13.6

CASE XX (Dr. C. P. Howard, Iowa City).—Female, white, 24. January, 1913. Enlargement of glands of left axilla noted. In February, 1913, glands of right axilla enlarged; also those of both sides of the neck and of the mediastinum. Gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 8, '13.....	4,780,000	20,000	90.4	0.4	0.0	2.4	1.4	0.0	5.4

CASE XXI (Dr. Yates).—Male, white, 37. Cervical glandular enlargement for twenty-one months. Removal of single glands at various times. Tonsillectomy June, 1913. December, 1913, large group of glands in left side of neck; no other enlargement.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 13, '13.....	Low	70.4	1.8	0.4	10.6	3.6	0.0	13.2

CASE XXII (Dr. G. E. Pfahler, Philadelphia).—Female, white, 22. Cervical glands noted in November, 1911. Subsequent involvement of mediastinal, mesenteric and retroperitoneal glands.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 10, '13.....	4,420,000	6,200	78.0	2.6	1.2	4.4	0.2	0.0	13.6

CASE XXIII (Dr. H. L. Ulrich, Minneapolis).—Male, white, 17. Operation for glands of the neck at age of 10. Operation at Rochester, November, 1912, for glands of neck. Diagnosis: tuberculosis. Gland removed in 1913; diagnosed at University of Minnesota laboratory as Hodgkin's disease. In December, 1913, enlarged glands in both sides of neck and in right axilla. Test gland shows unmistakable, typical well-developed Hodgkin's disease lesion.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 29, '13	10,000	60.4	2.0	0.6	20.8	6.2	0.2	9.8

CASE XXIV (Dr. Yates).—Male, white, 27. Glandular enlargement first noted in May, 1913. Marked enlargement of cervical axillary and mediastinal glands. Marked periglandular inflammation. Test gland shows intense and relatively acute reaction; but typical Hodgkin's disease features.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 20, '13.....	44,000	81.	1.6	0.0	8.8	0.4	0.2	5.0

CASE XXV (Dr. Yates).—Female, white, 17. Glandular enlargement first noted in September, 1913. Marked involvement of left cervical and axillary regions and of mediastinum. Well-marked periglandular reaction. Sclerosis of excised gland indicates greater duration.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 17, '14.....	15,000	72.6	0.9	0.4	15.3	3.0	0.4	7.4

HODGKIN'S DISEASE.[1]

By C. H. BUNTING, M. D.

(From the Pathological Laboratory of the University of Wisconsin.)

My interest in Hodgkin's disease dates from a series of experiments performed in the laboratory of Dr. Flexner at the University of Pennsylvania in 1903. In some of these experiments, the intraperitoneal injection of a lymphotoxic serum produced in the mesenteric lymph glands of the rabbits changes which were of the nature of the earliest changes in Hodgkin's disease; that is, there was necrosis of lymphocytes, proliferation of endothelioid cells, infiltration by eosinophiles and a proliferation of fibroblasts independent of the gross framework of the gland.

These results, coupled with the inability of those working on the disease at that time to find pathogenic organisms in

[1] Paper read at a meeting of The Johns Hopkins Hospital Medical Society, Feb. 2, 1914. The work forming the basis of this report has been aided by a grant from the Rockefeller Institute of Medical Research.

the glands, led to the development of a working theory as to the pathogenesis of Hodgkin's disease which I still hold, though in a modified form. This conception of the disease was, that the changes in the lymph glands were due to the filtration through them of a toxin elaborated at some primary focus of infection, and were in consequence entirely of a secondary nature—an end-result. For the explanation of the progress of the disease, I must introduce a subsidiary theory which seems borne out by pathological and experimental experience, that lymphadenoid tissue affords not only a mechanical, but also a chemical, filter for peripheral lymph, protecting the body cells generally and the red blood cells in particular, from a variety of toxins, at the expense of its lymphocytes. So in Hodgkin's disease, the primary group of glands, for a considerable length of time, protects the body from the toxin elaborated by the infectious agent. The removal of that group of glands by its ultimate sclerosis or by the hand of the surgeon, while the primary focus remains intact, exposes the body to an extension of the process to further glandular groups and, eventually, to an anæmia and a cachexia.

This theory slumbered until 1908, when, on my return to Wisconsin, I found that Dr. Yates was deeply interested in the disease, and we decided to join forces in an attempt to unravel its difficulties and to further its treatment. We have been handicapped throughout by the distance between us, and more by our inability to control a sufficient material for study. We have, however, through the kindness of friends in the medical profession, come in contact in one way or another with 28 cases.

From the standpoint of general etiology, the most striking feature of this series is that 13 of the cases were females and 15 males; and further, that while the males were, with but a single exception, under 34 years of age (and the exception but 35 at onset), the ages of 8 of the females ranged from 33 to 64 years. Both of these features are in contrast to Ziegler's[2] statistics derived from 210 cases gathered from literature. While it is dangerous to draw conclusions from a small series of cases, it would appear equally dangerous to follow Ziegler's method, if I may judge from a single case of which I have knowledge,[3] included in his series.

The study of these cases from a pathological standpoint has but strengthened the conviction that the lesion of Hodgkin's disease is essentially of inflammatory nature. The work of Reed and of Longcope leaves practically nothing of importance to be added to the description of the changes within the glands themselves, unless one emphasizes the fact that there are cases in which the disease runs so intense a course that the necrosis and the inflammatory reaction in the glands almost overshadow the more usually accepted chronic Hodgkin's disease picture. This appears to occur without secondary infection as far as cultures can determine.

[2] Die Hodgkinsche Krankheit, Jena, 1911.

[3] Among his cases of Hodgkin's disease of the spleen is included a metastasizing sarcoma of the spleen-pulp, published by me some years ago. In this case there was no involvement of the lymphoid tissue in the spleen or elsewhere.

Aside from the gland lesions there are, however, two points in the pathology of the disease which deserve mention. Careful search will, in the majority of cases, reveal a primary inflammatory lesion which was present before the enlargement of the glands occurred. In primary cervical Hodgkin's disease, this is most apt to be in the tonsils, teeth or nasal sinuses. In one primary cervical case, an otitis media of some duration proved the source of the infection. In a primary inguinal case the physician gave a history of a sharp attack of cystitis preceding the glandular enlargement. However, infection through the gastrointestinal mucous membrane is possible, as shown in cases in which the lesions are confined to the lymphoid tissue of the tract and the mesenteric glands.

The second point I wish to emphasize is that, while the glands in Hodgkin's disease remain discrete, they are, nevertheless, bound together in chronic cases by a mass of sclerotic tissue. In other words, there is in the disease an extraglandular inflammatory process which is of a relatively acute nature in early cases, showing a marked inflammatory œdema and a moderate and diffuse infiltration with polymorphonuclears, as well as with large and small mononuclears. There is an early stimulation of fibroblasts leading to the marked sclerosis of chronic cases.

That there is a general systemic reaction in Hodgkin's disease and not simply a process within a gland or group of glands is indicated by the changes in the blood picture, to which I have given considerable study, but to which I shall refer only briefly here, as I have considered them in detail in another paper.

A study of 25 cases shows that they may be divided into two groups according to their blood picture. The first of these groups includes roughly those cases of less than a year's duration, and the second, those of over a year's duration, although duration does not appear to be the chief factor in determining the blood picture. The blood in both groups shows a marked increase in blood platelets, with the presence of large platelet masses and megalokaryocyte pseudopodia. The only other constant feature is an absolute and usually a relative increase in the so-called transitional cell—the large mononuclear with indented or lobed nucleus and abundant protoplasm with azurophile granulation. This is Mallory's endothelial leukocyte, but I believe it is derived from the cells of the reticulum of lymphoid tissue rather than from the lining of the sinuses.

Except in these two points, the two groups of cases vary in blood picture. The first group shows little, if any, increase in the total leukocyte count; the second, usually a pronounced leukocytosis, even up to 100,000 cells per cmm. In the very early cases of the first group, there is a deficiency in eosinophiles, a slight increase in basophiles, and a fairly well marked lymphocytosis. This is followed after compensation by a slight eosinophilia, and by a gradual decrease in lymphocytes.

In the second group of cases, we have a neutrophile leukocytosis, the percentage of these cells ranging from 76 to 90 in the series. Lymphocytes are exceeded in number by the transitionals in 10 out of 13 cases falling in this group.

Those three may be the only varieties of cells found. The blood picture appears to be of diagnostic value in cases with chronic glandular enlargement; at least, the differentiation from tuberculosis of the glands is possible. I have not been able, however, to differentiate Hodgkin's disease from certain cases of the so-called malignant lymphoma by the blood smear.

In spite of the failure of others to obtain organisms in cultures from cases of Hodgkin's disease, Dr. Yates and I made efforts, wherever opportunity offered, to find by the cultural method the agent producing the disease. Our early efforts at operation and post mortem examination were failures. Our success in obtaining the organism, which we are convinced is the cause of the disease, was, I believe, the result of the following factors: Choice of a suitable medium, the implantation of large pieces of gland tissue with interglandular tissue, and incubation for a sufficiently long period. These steps were not adopted purely by accident. We felt that the organism was one of the so-called higher bacteria, if not a fungus, and consequently, selected cultural material suitable for the growth of the tubercle bacillus; *i. e.*, Dorsett's egg medium and glycerine-phosphate-agar. We further concluded that the organisms were few in number in the glands and were also difficult to grow, so slices of gland as large as the diameter of the test tube would permit were implanted, with the idea that in this way we should stand more chance of implanting organisms, and also with the thought of furnishing sufficient human proteid to give the organism a start at growth. Finally we sealed the tubes and incubated them indefinitely.

Our first successful implantation was made in February, 1912, when, after 10 days' incubation of tissue from a case, we found growth of a diphtheroid organism in 3 of 6 tubes and on both egg medium and glycerine-phosphate-agar. Since then we have not failed to find the organism in any active case of Hodgkin's disease (untreated by the X-ray), in which we have had opportunity to get cultures. It has been found by us, usually in pure culture, in cervical, axillary, and inguinal glands, and in the spleen. However, not infrequently in some tube a growth of a white coccus would be found, although every effort was made to prevent contamination from the skin of the patient operated upon.

The cultural method indicates that even in relatively acute cases the number of organisms in the glands is small. Growth may appear in but 3 or 4 tubes out of a dozen, and in any one tube there are but few colonies.

The organism grows feebly from most cases when first isolated, and may require careful nursing in order to secure a growth upon the medium independent of the human tissue. Two cultures, however, grew very luxuriantly from the start, and one of these we have used for our experimental work. Growth of this culture, however, was as difficult to obtain, after passage through the monkey, as in the majority of human cases.

The organism is Gram-staining and non-acid-fast, and its most striking feature is its pleomorphism. This is so remarkable that about six weeks were spent in an effort to separate supposed contaminations of the culture. The cultures on different media and at different ages show long, banded, and granular rods, fusiform rods, club shaped and large spherical involution forms, short, plump bacilli with polar staining, and coccoid forms. In the older cultures the coccoid forms predominate. Yet a fresh transfer of such coccoid forms will give, on suitable media, the characteristic, long, diphtheroid bacilli.

While one might not expect that an organism which did not produce death in human beings acutely, would be highly virulent to laboratory animals, yet our early experiments were disappointing. Large doses of 24-hour cultures appeared almost innocuous to guinea pigs and white rats. When recourse was had to the monkey, a similar disappointment was met with. By repeated injections, changes were produced in the lymph glands similar to those found in the glands in early cases of Hodgkin's disease in man. Yet the organism would not gain a foothold, apparently, and the glandular enlargement and the periglandular induration would subside. However, that difficulty was overcome. The first step was the recovery of the organism in pure culture from an abscess developing at the site of an inoculation two days before. This organism was then used for injection of the other monkeys. From one of these monkeys an enlarged gland was removed one week after inoculation in its vicinity, and was implanted subcutaneously into another monkey. This animal died in 10 weeks with marked involvement of its lymphoid tissue. The organism was recovered in pure culture and a small dose was inoculated into a monkey which had proved refractory to the original culture. This monkey died also, within 10 weeks, and with most marked lesions of its lymphoid tissue throughout.

One monkey finally became susceptible to the original culture and has shown progressive glandular enlargement since the last injection in August, 1913. Thus we have demonstrated the pathogenicity of the culture, but its virulence toward the monkey has been increased to such a point that the resulting lesions are of a very acute nature.

The elements of the Hodgkin's disease gland picture are present. One finds the marked proliferation of endothelioid cells, with endothelioid giant-cells, eosinophile infiltration, and a proliferation of fibroblasts. However, these changes are overshadowed by the extensive necrosis of tissue, and the polymorphonuclear leukocyte infiltration of the necrotic areas. These areas appear to be made up chiefly of the newly proliferated endothelioid cells. While this picture may seem quite different from that seen in the more chronic cases in human beings, we have recently had its counterpart in a patient with Hodgkin's disease in whom the course of the disease was of a relatively acute nature.

I have been impressed, also, by the fact that in the monkeys inoculated with the organism of increased virulence, the pathological changes in the lymphoid tissue are in many features strikingly like those described by Councilman, Mallory and Pearce in human cases dying of diphtheria. As a result of these experimental studies, and of the incomplete observation of certain clinical cases, I believe we shall

find that some obscure infections in man resulting in extensive subcutaneous inflammatory reaction without pus formation, and in intense glandular reaction, will be proved, upon bacteriological investigation, to be cases of acute Hodgkin's disease.

There is one other relationship of Hodgkin's disease that needs mention. Morphologically there is great difficulty in diagnosing between various types of so-called malignant lymph gland lesions. As I have mentioned earlier, in a case of malignant lymphoma, with a primary, slightly greenish tumor in the orbit, and with general glandular and splenic enlargement, the blood picture was identical with that in Hodgkin's disease. Furthermore, a culture was obtained from the glands in this case of an organism quite similar to, if not identical with, that obtained from cases of Hodgkin's disease. Billings and Rosenow have also reported the cultivation of a diphtheroid organism from a case diagnosed histologically as lymphosarcoma. In the chloroma case there was noted at operation, also, the same marked interglandular sclerosis seen in Hodgkin's disease. These findings practically force the suggestion, open to further proof or disproof, that these diseases differ but quantitatively and not qualitatively.

To summarize our picture and revise our theory, Hodgkin's disease is an infectious disease due to a diphtheroid organism, the *Bacterium Hodgkini*. There may often be found a primary lesion at the portal of entry. While in some cases the organisms may remain for a long time localized in the vicinity of the portal of entry, in other cases they early gain entrance into the general circulation, and may be widely distributed. The organism and its toxin show a special affinity for lymphoid tissue, and produce in this the characteristic changes of Hodgkin's disease, changes varying somewhat according to the intensity of the toxin, but resulting ultimately in the sclerosis of the glands. There is at the same time an interglandular inflammatory process, at times very acute, but resulting finally in a dense sclerotic tissue. There are also characteristic blood changes in the disease.

The glandular changes can then be considered only as the result of a toxic action, and contribute to the patient's death merely incidentally, when certain gland groups are extensively enlarged. The cells of the enlarged glands, though atypical, show none of the antagonism to the other body cells characteristic of malignant neoplasms.

A CLINICAL CONSIDERATION OF HODGKIN'S DISEASE.*

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This communication is based upon studies made during the last six years in conjunction with Dr. C. H. Bunting, of Madison, Wis., and is to be regarded as both elementary and preliminary in nature.

Definition.—Temporarily Hodgkin's disease may be considered an infectious, non-contagious affection due to the *B. Hodgkini*. It is characterized by a somewhat variable, though definite, reaction in the lymphatic and perilymphatic structures, specific changes in the blood picture and by the manifestation of little or no tendency to spontaneous recovery.

Diagnosis.—Heredity and contagion have little, if any, significance in the history. The sexes are equally represented (16 males, 15 females) between five and sixty-four years with an apparent tendency to appear comparatively earlier in males and later in females. As a rule there is disclosed nothing sufficiently definite symptomatically to indicate the time of infection or the portal of entry. Enlargement of the cervical glands is commonly noted as the first evidence of the disease, and is usually discovered by chance during a period of well being. Infrequently this glandular enlargement is preceded by a sense of lassitude, or there may have been a well-defined, if not severe, irritation in the throat, nose, eye or ear. Glands in the lower posterior cervical triangle are more commonly noted primarily than those higher up, further extension taking place, in order of frequency, to the axilla on the same side, to the opposite cervical region, the mediastinum, the opposite axilla, to the groins and the peritoneum, the spleen and liver. Primary involvement in the inguinal glands has been noted as following cystitis and leucorrhœa or has appeared without the least evidence of any exciting cause (lymphosarcoma?). In acute cases the enlargement of glands first affected, and the subsequent extension to other members of the same group and to other groups of glands may be rapid and rather steadily progressive. Perhaps more often there are alternating periods of enlargement and regression even in the acute type. During the periods of enlargement (this is noticed by the more observing patients) the individual glands seem partially to lose their identity, the whole group becoming fused into a nodular mass. This may lead to bogginess in the subcutaneous tissue or even to redness and edematous induration in the skin. Excision of tissue and subsequent microscopic study by Dr. Bunting has demonstrated that these changes are due to waves in the acuteness of the periadenitis, rather than to increased adenitis and may have an important bearing upon the question of treatment. Early bad effect upon the general health is attributable to toxæmia which is always sufficient to affect the blood picture. During intervals of regression in the glandular enlargement there is apt to be a sense of greater well being, with a corre-

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sponding sense of lassitude when there is an increased enlargement. Thus it may be suspected that there are waves in the toxin production.

Later appears the secondary anæmia due probably to an hemolysin produced by the organism, and rarely, spontaneous recurrent hemorrhages from some of the mucous membranes resulting from an absence of the blood platelets caused by exhaustion of the bone marrow. The Pel-Ebstein type of recurrent fever, seen late in the disease, need not be due to any intercurrent infection and has thus far indicated a hopeless prognosis.

Death may result from grave anæmia, cachexia, obstruction to respiration, to the circulation or to pressure upon the thoracic duct with consequent chylous ascites or to a combination of these factors. It is commonly supposed to occur in from a few months after onset to within five years but to be inevitable.

An absolute diagnosis cannot be made without laboratory assistance in the histological and bacteriological examination of the blood and excised tissue. So positive a statement demands some explanation.

Hodgkin's disease may simulate tuberculous adenitis so closely, even to involvement of the preauricular gland that clinically they may be indifferentiable. Lymphatic leukemia, believed by Cohnheim and Wunderlich to be but a stage of pseudoleukemia or Hodgkin's disease, made a transient appearance in the course of one case under our observation, an extremely significant observation, particularly if the organism isolated by Steele * from a lymph gland in that condition should prove to be the *B. Hodgkini*. In one case of chloroma and two cases of lymphosarcoma (clinical and histological) Bunting has diagnosed Hodgkin's disease by a blood count and found confirmation in positive cultures from the excised tissue. Rosenow † obtained the diphtheroid organism from a tissue histologically diagnosed lymphosarcoma.

Complications.—Tuberculosis has been unexpectedly infrequent. In but two instances has there been a positive von Pirquet reaction, one with a limited apical lesion, one (lymphosarcoma) with none demonstrable. One case had secondary lues. Terminal acute infections are perhaps the rule.

Blood.—In spite of Dr. Bunting's work (Johns Hopkins Hosp. Bull., 1911, XXII, 114) on the blood picture in Hodgkin's disease, it is almost universally accepted that there is manifested herein, nothing essentially or constantly characteristic. We have had repeated opportunity in the past six years to test out the accuracy of this observation of Dr. Bunting's and have no hesitation in stating most emphatically that, in his hands at least, a differential blood count is the surest and the quickest method of establishing a diagnosis. During this time repeated attempts have been made to confuse and to confound Dr. Bunting by submitting to him unidentified blood smears from individuals suffering from other maladies with and without adenopathies, and thus far his differentiation of Hodgkin's disease has been correct with but a single exception and that early in the work and in a case complicated by a terminal intercurrent infection. One cannot overestimate the importance of these blood examinations for by them, as will be shown later, some guide can be found as to the efficacy of the treatment and they afford the only sure way to determine ultimate recovery.

Cultures.—When the specific organism can be isolated, a diagnosis is established, no matter what may be the histological picture of the affected tissue. Until the occurrence of the organism in various borderline affections has been determined and thereby the lesions that it may cause have been recognized, its presence must be accepted, until the specificity of the blood picture is established, as the one irrefutable diagnostic feature.

Excised Tissue.—A diagnosis of Hodgkin's disease from a section showing the changes described by Reed could no longer be questioned. It will be some time before an equally positive diagnosis can be made in sections showing changes long supposed to indicate other affections, *e. g.*, certain types of leukemia, lymphosarcoma or chloroma. For the present negative histological evidence must, to some extent, remain inconclusive.

Attempts are being made to develop some form of a diagnostic skin reaction, but so far the results are too inconstant to be reliable. Specific agglutinins have not been found.

Treatment.—The hopelessness of the disease has seemed to warrant recourse to any therapeutic measures that have promised even temporary relief. On the other hand, we have attempted nothing that appeared irrational in the light of the progress of Dr. Bunting's brilliant and thorough investigations. During four years of futile search for the causative agent, we were misled into blind alleys, but happily none was harmful in results and each taught its invaluable lesson as to those things not to do, some of which will be mentioned to safeguard others. If any progress has been made or is to be made in the treatment of Hodgkin's disease it must be through a rational clinical application of laboratory observations.

Observation of cases over a considerable period has taught that successful treatment is dependent upon unremitting watchfulness, and the forehanded recourse to every precaution to establish and to keep the balance of power on the side of the individual against the virulence of the infection, which, notoriously insidious in its onset and ruthless in its initial progress, is often even more so in recrudescence.

Cases can be classified primarily as favorable or unfavorable upon the basis of the evident relative virulence of infection and by the nature and distribution of involvement, rather than through the extent to which individual groups of glands have become affected. Slower growing glands with a tendency to remain discrete are more favorable even when involving multiple groups, for example, both sides of the neck and an axilla, than those exhibiting a tendency to become coalesced and adherent to the skin through repeated exacerbations in periadenitis, even though but one supraclavicular group be manifestly affected. It is the latter type which is so prone to early mediastinal invasion and to general hematogenous dissemina-

* Boston M. & S. J., 1914, CLXX, 123.

† J. Am. M. Ass., 1913, LXI, 2122.

tion with intraperitoneal involvement. Mediastinal infection is almost, and intraperitoneal extension is certainly, of hopeless prognosis and must so remain until more efficacious methods of treatment are developed.

The following treatment which has been and still is being developed is based upon this philosophy: fostering localization of the infection with earliest possible elimination of the same. The therapeutic procedures are regarded as primary and supplementary and have been applied as will be indicated to favorable and unfavorable cases.

Primary Procedures.—Portals of entry in so great a majority of individuals are to be found in the mouth, throat, nose and ear, that routine radical tonsillectomy, competent investigation and treatment of teeth, accessory nasal sinuses and ears are prerequisites and should often include skiagraphy.

The demonstration by Dr. Bunting of lesions of Hodgkin's disease, of the unmistakable Dorothy Reed type, in tonsils manifesting little, if any, abnormality, *in situ*, has confirmed the propriety of this attitude. In addition the likelihood of dissemination from these foci through the circulation, especially the lymphatic, is notoriously great. Organisms resembling *B. Hodgkini* morphologically have been observed in abscesses about the roots of teeth and in the discharges from nasal sinuses. The danger of gastrointestinal and even peribronchial infection from such sources is real if slight. Any real danger in this disease, be it however slight, is a grave danger and neglected may determine a fatal issue otherwise avoidable.

Surgical removal of the greatest portion of the disease that can be accomplished with safety, gentleness and thoroughness as advocated by Halsted in extirpating cancer, appears to do most to throw the balance of power in favor of the individual. This is always to be done after recovery from tonsillectomy which is best accomplished, when possible, under local anesthesia. Virtually as complete an excision as that advocated by Crile in cancer of the cervical glands should be made, for involvement is always wider than appears externally and has often extended to all the regionary glands. When excision is incomplete, recurrences are generally prompt and these early recurrences usually manifest decidedly increased virulence. Since the microorganisms are probably present in the periglandular tissue, it is impossible to overestimate the importance of thoroughness, gentleness and the sharpest possible dissection and of not operating during a period of acute periadenitis. It is, moreover, inconceivable under any condition that the field of operation could remain uncontaminated. This, therefore, should be thoroughly treated with tincture of iodine and drained. The immediate reaction is greater and the healing not so smooth but the tendency to recurrence is definitely reduced. Incidentally scar tissue is notoriously poor soil for the persistence of infection. A patient's resistance is not long or materially reduced by this type of intervention and there is a deal of comfort in the realization that many bacteria and their toxins, together with degenerate tissue the result thereof, are truly innocuous *in vitro*.

One emaciated child of five succumbed to an ill-advised operation. One woman died from an anesthetic before an operation to decompress her mediastinum could be begun. With these exceptions, not even many repeated interventions on the same individual have been followed by more than temporary distress, and not to our knowledge has the course of the disease been unfavorably affected by surgical work when done according to the principles enumerated above. On the other hand excisions and re-excisions are commonly followed by improvement other methods have failed to achieve.

Supplementary Procedures.—The whole area of operation should be subjected to X-rays, in measured doses, begun the same or the first or second day after excision and repeated thereafter as frequently and for as long a time as safety permits. Wherever else the disease is present or suspected, should be also thoroughly treated. Dr. Foerster and Dr. Baer have spared neither time nor pains in cooperating in this work and it is quite impossible to estimate how greatly these patients, nearly all of them indigent, have benefited by their generous attention.

Control observations from the same individual indicate that it is impossible to obtain cultures from glands after they have been thoroughly X-rayed, that such glands and periglandular tissue show increased sclerosis with the appearance of more giant cells and hyaline degeneration within the glands. Moreover, individual glands, and those in chains and groups, that have been shown histologically to have been the seat of definite Hodgkin's disease have disappeared more or less completely and remained stationary for two, three and five years after X-ray treatment given subsequent to the removal of exciting foci. No such result is unfortunately as yet to be recorded in retrosternal involvement.

Vaccine.—Our experience is too limited to make possible any statement as to curative results from this treatment. Each case receiving vaccine treatment is being followed with repeated blood studies by Dr. Bunting, who is kept in ignorance of the source of the specimen and the nature of the treatment. Unquestionably there may be temporary subjective and apparently objective improvement attributable to the vaccine. Certainly there may be actual harm done even with small doses. We believe that until more is known of the late and permanent results of vaccination it is essential to regard this as a part of a method of treatment, be it curative or prophylactic against recurrence, which is as yet of insufficiently demonstrated value.

Serum.—A startling similarity, noted by Bunting in the lesions of the experimental disease in monkeys, in very acute human disease and in those occurring in fatal diphtheria, together with the diphtheroid type of organism, suggested a possibility of benefit to be obtained from administration of diphtheria antitoxin. This has been given adequate trial. Some subjective and possibly some objective improvement followed its use. This questionable improvement was transient at best and nothing to warrant its routine administration was noted. The serum was assumed to be without any specific action.

Comparison of three varieties of antitoxic serum and one normal horse serum as to bacterial agglutinins and lysins for different strains of *B. Hodgkini* and *B. diphtheriæ* disclosed no regularity in action.

Transfusion has not been found to be of any lasting value, not even in the presence of spontaneous hemorrhages as it was impossible after repeated transfusions, to restore the platelets to the circulation.

Drugs.—Persistence of the arsenical superstition, together with a temporary suspicion that the disease was due to a fungus, led to the administration of salvarsan intra-muscularly and intravenously. In febrile cases it may reduce the temperature to normal for a day or two, and even cause splenic and hepatic enlargements to diminish materially but only temporarily. It was without appreciable effect upon the ultimate outcome. Tonics are often of a great service, but arsenic no more than iron. Benzol has not been given.

Hygiene.—Too much importance cannot be attached to maintaining these individuals upon the highest possible level of general physiological efficiency. Recurrences are prone to appear upon the wake of any considerable or even slight phase of deficiency. Mental depression over a short period has seemed sufficient to induce a recrudescence.

Recurrences.—Glands have been repeatedly excised from regions (necks and axillæ), previously operated upon, which have finally remained free from any evidence of disease, some for upwards of three years. In one individual, with a late return (four years), glands excised showed but an ordinary chronic adenitis, indicating strongly the probability of local cure, after two previous operations when tissue excised was histologically that of Hodgkin's disease. Another patient upon three occasions became slightly febrile with recurrences of only an axillary gland or two in each instance, but the temperature returned to normal promptly after their excision. Moreover, later recurrences manifest a tendency, if the histological picture be a criterion, to exhibit an increasing chronicity in the process.

It is impossible to forecast what any recurrent gland will do under otherwise favorable conditions and under any form of treatment save that even a small one may act as a primary focus in the dissemination of both toxin and infection. It is best, therefore, to excise the gland under local anesthesia, which can be done safely and with trifling distress. The surest remedy is self-evident—a course of X-ray exposures is again to be instituted as if it were a primary operation. It is probable that this treatment should be repeated periodically as a prophylactic against recurrence.

Unfavorable Cases.—We are attempting to institute such supplementary procedures as eventually may make the application of more definitely curative primary procedures possible and justifiable.

That progress in dissemination which typifies Hodgkin's disease may be likened to a row of children's blocks. If the first be upset unless the sequence be broken the whole series will fall. Unfortunately, in this disease, merely breaking the sequence may avail little as any hiatus is more than likely to be crossed, if in addition, the upsetting force be uncontrolled. Probably no part of the chain is more vicious than the initial lesion which should therefore be eliminated if conditions permit. Usually this is demanded if anything is to be attempted in the line of curative therapy.

Any or all methods of combined treatment frequently retard the progress of the disease, indeed may even induce a protracted regression with a prolongation of a relatively comfortable and hopeful existence.

This much is at present attainable and optimism indicates the future possibility of some recoveries even under these adverse conditions, as a stimulating encouragement—at least one may find comfort in the knowledge that the mortality rate cannot be increased.

Results.—Early Hodgkin's disease, at least that form exhibiting the changes described by Reed, is curable if spontaneous recovery seldom or never occurs.

A cure or recovery we consider as established only when an individual shows no trace of the disease, and has a normal blood picture, four to five years after manifest glandular enlargement has disappeared. This extreme position is justified by the knowledge that recrudescence can occur after a shorter period of apparent freedom from disease. Upon this basis, we have but six cases to report:

CASE I.—June, 1908. R. B., female, æt. 32. Duration over a year. Seen two days before death. Very extensive involvement; most intense distress which was uncontrollable by opium. Death due to anesthetic given in an attempt to decompress mediastinum which was filled with a mass of glands almost as large as the heart itself.

CASE II.—October 8, 1908. W. R., male, æt. 10. Duration one year. Left side of neck from mastoid to below level of clavicle and from midline in front to behind anterior margin of trapezius occupied by mass of glands, not coalesced, not adherent to skin.

October 10, 1908. Complete excision. Positive Hodgkin's disease histologically. Cultures negative. Prompt recovery. Smooth healing. X-ray treatment begun and continued.

June 24, 1909. Began to look and feel badly. Recurrence in region of submaxillary gland. Has not been rayed recently.

August 15, 1909. Recurrence. Excision. Histologically Hodgkin's disease. Recovery smooth. X-ray started again.

October 22, 1910. General condition excellent. Slightly enlarged glands at tip of hyoid process and at outer margin of base of mastoid. Chest and abdomen negative.

July 1, 1913. Two more glands present in region of submaxillary. Those noted above, present and unchanged. All excised. All negative histologically.

January 27, 1914. Apparently well on critical physical examination. Blood count indicated recurrence which was disclosed by stereoscopic X-ray (Eisen) in a gland lying behind the left sternoclavicular articulation.

March 9, 1914. General condition excellent. Has been getting polyvalent sensitized vaccine (Rosenow). Gland increasing in size.

CASE III.—October 9, 1908. W. B., male, æt. 33. Duration six months. Itching of skin was first symptom. Dense fist-sized mass in left supraclavicular region. Overlying skin boggy. Smaller mass in apex of left axilla. Dullness over upper mediastinum. Treatment refused. Took several courses of X-ray treatment with little effect. Mud baths were curiously without beneficial result.

April 20, 1909. Death. No necropsy.

CASE IV.—October 30, 1908. K. F. B., male, æt. 22. Nasopharyngeal irritation six months before. Felt off color. Recently noted few enlarged bilateral cervical and axillary glands. Mainly in posterior triangles. Groins, abdomen and chest negative.

November, 1908. Glands excised for diagnosis. Positive Hodgkin's disease. Tonsillectomy followed by X-ray treatment. Hygienic measures.

December, 1912. Few glands smaller than peas in left posterior triangle, one gland smaller than pea in right posterior triangle. Axillæ similar. Groins and abdomen negative.

January, 1914. Reported to Dr. Bunting. Health excellent. Blood picture normal. It was from the study of this blood previously that the characteristic blood changes were recognized.

Case V.—September, 1909. G. R., male, æt. 8. Enlarged glands noted by public school nurse eight months before. No effect on general health. History unimportant. Large mass of glands below angle of left jaw. No general glandular enlargement. Chest and abdomen negative.

September 30, 1909. Gland removed for diagnosis. Positive.

November 15, 1909. Cervical mass excised. Marked periglandular sclerosis. Incomplete operation. Tonsillectomy. X-ray and hygienic treatment.

September 7, 1910. Recurrence noted beneath angle of jaw. Excised. Positive Hodgkin's disease.

October 8, 1910. von Pirquet test negative.

November 25, 1910. General condition excellent. No recurrence. Mediastinum free.

February 9, 1911. General condition good. Small glands in both sides of neck and both axillæ.

March 7, 1911. Readmitted to hospital because of profuse nosebleeds. Coagulation time six to seven minutes. Subsided under rest and administration of horse serum (?).

April 20, 1911. Again admitted to hospital. Bleeding from nose and gums. Anæmic. Febrile. Spleen enlarged. Abdomen distended. Transfused—mother.

May 1, 1911. Again transfused—mother.

May 9, 1911. Again transfused—brother.

May 17, 1911. Onset of first marked attack of continued fever.

May 22, 1911. 0.3 gm. "606" in buttocks. Some effect on temperature.

June 15, 1911. Recurrence of febrile state. Given 0.3 gm. "606" intravenously. Reduction of temperature but for two days only. Decrease noted in size of spleen and liver which had lately become enlarged.

July 22, 1911. Another attack of Pel-Ebstein fever with epistaxis. Liver smaller, spleen same size.

August 21, 1911. Recurrence of fever. Spleen large, liver smaller.

September 1, 1911. Only evidence of disease in glands in group about submaxillary. Excised. Positive Hodgkin's disease. Emulsified and injected into guinea pigs. No effect. Cultures: White coccus and *B. subtilis*.

September 20, 1911. First recurrence of fever since operation. Bleeding from nose and gums.

October 16, 1911. Fever continued. Rapid local recurrence of gland under ear. 0.2 gm. "606" intravenously without effect.

January 23, 1912. Gradually failed. Increasing emaciation and abdominal distension. Death from starvation. Necropsy—chylous ascites. Advanced retroperitoneal lymph gland involvement. General wasting. Anæmia. Cultures—contaminated.

Case VI.—December 2, 1909. F. v. S., male, æt. 10. Under nourished. Slightly enlarged glands both sides of neck, both axillæ and both groins. Abdomen negative. Harsh and prolonged expiration at left apex. Blood positive Hodgkin's disease.

January 10, 1910. Tonsillectomy. Glands for diagnosis from groin, neck and axillæ. Cervical glands positive Hodgkin's disease. X-ray and hygienic treatment.

April 26, 1910. Slight glandular enlargement persists. Growing rapidly and gaining in weight.

October 5, 1910. Still gaining. von Pirquet test positive. Glands remain the same.

September 10, 1913. Glandular condition about same. Harsh breathing at left upper. von Pirquet test positive. Few slightly enlarged glands palpable.

January 6, 1914. General condition excellent. Blood picture normal. Glands quiescent.

Obviously so small a number of cases is of little value, save in the lessons to be learned from mistakes.

Case I was virtually dying. Intervention was prompted only by desire to relieve a degree of distress too great to admit of description. Treated early in the disease, the outlook would have been excellent.

Case III, almost certainly hopelessly involved when first seen, possibly illustrates the impotence of the X-ray to control the progress of the disease so long as the primary focus and the major portion of the disease remains. Prognosis was probably bad from the outset because of early extension of the disease to the mediastinum.

Case V illustrates the harmful results of incomplete surgical intervention. This boy was of the puny type and a congenital pessimist. Had better judgment prevailed and the slightly added risk of a complete radical excision been accepted primarily, it is conceivable that this life might have been saved.

Case II, apparently more unfavorable than Case V primarily, was treated the more radically because of supposed hopelessness otherwise. This child was discouragingly puny, but an aggressive optimist. First recurrence (9 months) accompanied evident deterioration in general health with prompt improvement following excision. Suspected recurrence three years after the first was unaccompanied by any effect upon general health. Microscopic examination proved these glands to be free of changes due to Hodgkin's disease. Finally four and one-half years after last positive evidence of the disease was found, while feeling perfectly well and after repeated physical examinations with special attention directed to the mediastinum had failed to disclose any evidence of disease, a routine blood examination indicated a recrudescence. Stereoscopic skiagrams revealed glandular enlargement behind the left sterno-clavicular articulation. The primary operation had extended down to the region of the thoracic duct, indeed it was probably injured and ligated.

Cases IV and VI, both nephews of physicians were given every benefit of early and late treatment and serve as proof that the disease is curable without the aid of any specific therapy.

In conclusion even these few cases indicate that primarily Hodgkin's disease is a localized process, susceptible of cure when properly treated as a malign, though chronic infection. It may persist for years without manifesting itself save in the blood picture so that cures may not be assumed until after an uninterrupted duration of years of persistently normal conditions.

A sovereign remedy for all cases is not now conceivable. At present the greatest need is some therapeutic agency to control glands not directly accessible; for once extension, which may occur early, has reached either the thorax or abdomen the prognosis becomes relatively, if not absolutely hopeless.

SOME UNPUBLISHED WATER-COLOR SKETCHES OF SIR CHARLES BELL,* WITH OBSERVATIONS ON HIS ARTISTIC QUALITIES.†

By EUGENE R. CORSON, M. D., Savannah, Ga.

I bring these unpublished sketches of Sir Charles Bell before the profession, first, with the hope, that it may induce others better situated than myself to publish other sketches of his, both drawings and paintings, stowed away in England in museums, and out of the way places, perhaps, whose publication at this time, when photography is so universal and the free hand of the true artist so rare, should stimulate us to more artistic work in anatomy and medicine generally. And, secondly, because I believe a study of Sir Charles's artistic work will attract us to the relationship of Art to Medicine, give an added impulse to the study of artistic anatomy, and show wherein we may improve our methods in the mere study of anatomy itself.

To call these sketches, which I have the honor and the pleasure to present to you, "unpublished" demands some qualification. They have never been reproduced as such, but they were provisional sketches to serve as "copy" for his etchings in his work on the arteries, the first edition of which appeared in 1801. But the very fact that they did serve as provisional sketches makes them, in my mind, of greater value, for they show Sir Charles's methods of work, and exemplify certain principles in anatomical delineation well worthy of our consideration.

In a letter to his brother George, written on January 8, 1805, he wrote:

> I am doing my sketches in water-colours complete, out and out, leaving it for after-determination how they may be engraved.

The majority of the sketches were done about or before 1800 and these words apply equally well to them. With the instinct of the true artist he must try out by sketch before attempting the finished picture; and comparing the two before us, we see how he worked and wherein the finished picture excelled or missed the excellence of the first sketch. Sir Charles has himself well contrasted the sketch with the finished picture in his "Anatomy of Expression," when treating of the uses of anatomy to the painter. He writes:

> It is true that the sketch is too often a mere indication of the painter's design, intended to be worked up to the truth of representation as he transfers it to the canvas—that the outlines of the figures are rather shadowy forms, undefined in their minute parts, than studies of anatomical expression, or as guides in the subsequent labour. And, perhaps, it is for this reason that there have been many painters, whose sketches all admire, but whose finished paintings fall short of public expectation. But a sketch that is without vigor, and in which the anatomy has not been defined, is a bad foundation for a good picture; and even a little exaggeration in this respect is not only agreeable, but highly useful. The anatomy should be strongly marked in the original design; and from the dead coloring to the finishing, its harshness and ruggedness should be gradually softened into the modesty of nature. The character of the sketch is spirit and life; the finished painting must combine smoothness and accuracy. That which was a harsh outline in the sketch or the strong marking of a swelling muscle, or the crossing of a vein will be indicated in the finished composition, perhaps, only by a tinge of color. The anatomy of the finished picture will always be most successful, and even most delicate, when the painter has a clear conception of the course and swelling of each muscle and vein which enters into the delineation of the action.*

Of these twelve water-colors the plates marked II and IX are supposedly by Charles Cheney; Plate II, the plan of the aortic system, might well be left to a favorite pupil or assistant. Figure 2 on Plate IX, representing a hand with the index finger resting on a book, which figures in the third edition of the engravings is designated as drawn by C. Cheney and etched by Charles Bell. The etching is somewhat larger than the sketch, and a decided improvement over it. Like Figure 3 in Plate VIII it is a much later sketch, and done on a free space on the paper used years before.

Plates XI and XII, which appeared in the first and second editions, were replaced by four much better illustrations in the third edition.

Plate VIII, which consists of three figures, appears in the third edition as a plate of one figure. In the first and second editions Figures 1 and 2 appear without Figure 3, while in the third edition both Figures 1 and 2 are withdrawn, and the dissected arm, of which Figure 3 forms the proximal end, is alone given. I should therefore say that probably Figure 3 was painted much later than the other figures and that the etching was made direct from the dissection. In other words,

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* These sketches were bequeathed by the late Dr. Thomas Windsor, of Manchester (see British Medical Journal, London, June 11, 1910), to the Library of the Surgeon General's Office, Washington, D. C., and he was undoubtedly influenced to make this bequest through his friendship for the late Dr. John S. Billings, at one time its librarian.

The twelve plates are most of them 10½ by 8 inches in size, in water-color, showing the high coloring and free brush work of a preliminary sketch, striking specimens of free-hand drawing direct from the dissection. They were drawn undoubtedly before or about the year 1800, when Sir Charles was still in Edinburgh working with his elder brother John, for with the accompanying explanatory script of the plates they form the "copy" for the first edition of his "Engravings of the Arteries," published in 1801.

Changes and additions were made in subsequent editions, especially in the third, which bears the date 1811, when the negro's head and the two plates designated as drawn by C. Cheney, were introduced. As frequently happens, the pupil, drawing under the eye of the master, copies him, while the master's own touches make the picture more the master's than the pupil's. Sir Charles, to compliment a favorite pupil, designates him as the artist. So I interpret it.

† Paper presented at the XVIIth International Congress of Medicine, London, August 6-12, 1913. Section XXIII, History of Medicine.

* "The Anatomy and Philosophy of Expression as Connected with the Fine Arts," by Sir Charles Bell, K. H., 6th Edition, London, 1872, p. 227.

Figures 1 and 2 were drawn from dissections done in the early Edinburgh days, while Figure 3 is later London work, and indicates that he considered the dissection better adapted for his etching. It all shows his careful selection.

In Plate V, Figure 2 is reproduced, while Figure 1, which appears in the first and second editions, is replaced by another drawing to show the arteries of the face.

With these changes, the drawings have been reproduced by engraving or etching, and done by himself, with the exception of Plates II, III and X, which were etched by J. Stewart.

The accompanying script which is his own handwriting, in my judgment, is the script of a copy-book, written with great care and deliberation, when time seemed no object, but only the wish to produce an accurate and beautiful "copy" for the printer. It is like the delicate, precise handwriting of the Latin races. Throughout his life his handwriting changed but little; even when it shows rapidity, it is a beautiful flowing script, quite Spencerian in its curves and hair lines.

Examination of these sketches with a magnifier shows rapid work, with much of the drawing done with the brush itself. I see no pencil marks showing any drawing before taking up the brush. Even the coursing of the vessels is largely, if not wholly, rapid brush work, especially the smaller ramifications. The general outline of a head will be drawn with the brush, rapidly, and with a bold and free sweep. There is no hesitation anywhere, and he is sure of his drawing. He is not making any pictures, to be reproduced as such, but simply feeling his way to the more careful and accurate etching; and I cannot but believe, too, that the etching itself is made with the dissected part before him. John Bell ever insisted upon a careful copying of the dissection, and he taught this lesson to his younger brother with his wonted insistence and emphasis, and that Sir Charles learned his lesson well we have good evidence. Alluding to these very plates, he wrote: "I have etched most of the plates with my own hand, preferring accuracy to elegance."

While it was very evident from his published drawings how prolific his artistic work was, and how great his industry, these sketches give even better evidence of his rapidity and facility. In his first published work, *A System of Dissections*, there are many beautiful plates on a larger scale, which could have been easily reduced for the smaller work; but, no, his artistic sense and energy demanded new drawings and fresh dissections, and so we have a series of entirely different illustrations, additions, and improvements in the third edition which make it almost a new work. This in itself shows the artist and the man of science.

A comparison of the sketches with the etchings show some interesting and suggestive differences. Generally speaking, it may be said that as illustrations of dissections there is deterioration in the etchings. In the first place, five of the plates are much reduced in size. Size is an important factor in artistic conception, and in the grasp of the architectonic plan of any structure. Reduce Michael Angelo's David or the Venus of Milo to a one-foot figure, and no matter how perfect the reduction, how much is lost! Great as the drawings of Vesalius are as faithful copies from nature, and especially so when compared with the work of his predecessors, much of the effectiveness of the faithful copy is lost in the small size. Even his imitators, who simply enlarged these drawings, took a great step forward. We turn the pages of the *De Humanis Corporis Fabrica* more quickly than the pages of the *Tabulæ* of Albinus. Compare Sir Charles's small etchings of the arteries with Maclise's life-size drawings in Quain's splendid work. The etchings are more finished and delicate, but much less effective than the drawings of the less gifted artist, and almost entirely on account of the size. Of course the two works had different objects in view.

The trend of anatomical illustration is towards larger figures. Where the etching is the same size as the original sketch we can see the improvement from more careful drawing, and the greater distinctness of black and sharp lines. He was undoubtedly influenced in the small size of the other sketches by the subsequent etching. In the reproduction of Plate V Sir Charles himself, still influenced by the size of the prospective volume, has committed the error, rare with him, of overlooking the value of relationships in anatomical delineation, for in etching the arteries of the face, he has omitted the great trunk in the neck, well shown in the original sketch, and has etched for us a head cut off close to the base of the skull. A lack of proper relationships is worse than poor drawing. Sir Charles, of course, takes no liberties with his "copy"; he is always the faithful copyist. But J. Stewart, who etched Plate III, instead of faithfully copying the right iliac crest, as drawn for him, has seen fit, while Sir Charles's back was turned, to take every liberty with it, and he has given us a strangely scolloped bone. He also omitted the os pubis and ischium, which are in the original, and which give us the relationships of the iliac and beginning femoral arteries. He has, however, introduced the skull, omitted in the sketch, which shows he had the anatomical preparation before him.

While in a few instances the etched artery is better defined than the vessel drawn with the brush, it usually suffers in comparison, for the painted vessel is well accentuated, and even exaggerated. Exaggeration, when properly applied—for only the real artist can use it correctly—is a true principle of art. The Greeks had the audacity to increase the facial angle, and with what marvelous effect! The genius of Michael Angelo put its own limits on bony prominences and swelling muscles, and his drawings and plastic art are good anatomical models to-day.

The sketches, as well as the etchings, show an ever present sense of the third dimension. His drawings are never flat. Even in his descriptions of the ligations of the arteries, he is ever mindful of their depth. On this point examine Plate II (Third Edition), showng the femoral with its profunda branches; the drawing is almost stereoscopic. Many beautiful examples could be given to show this quality.

In a general way, it can be seen that Sir Charles has followed the principle which he sets forth in the essay from

which I have quoted, namely, that the anatomy should be strongly marked in the sketch, and in the finished picture "should be gradually softened into the modesty of nature." While this was probably the prevailing idea one hundred years ago, I am sure the best artists of to-day would modify it. Sir Charles strikes the real key-note of all anatomical delineation when he writes: "The character of the sketch is spirit and life." Art is the expression of life, and the more true and intense this expression, the more artistic. If the artist paints the dead body, it must suggest the life which has flown. If he paints the dissected body, the more clearly he shows us the parts in their true relationships with their relative values, *the more does he suggest their function*, and the more artistic does his work become. The conception cannot be too comprehensive, or too general; never yet has its deepest depths been sounded, and never yet has its surface been ever so lightly touched without some artistic response. Sir Charles, of course, is writing of art in general, and this principle is in a way more applicable there than in anatomical delineation proper. But in all his writings and in his most pretentious drawings, his aim ever was to raise anatomical and clinical drawings to a higher artistic level. He writes in one of his letters to his brother George: "Sometimes I think of finishing my anatomy of the muscles in painting in great style." This was a great idea and we should endeavor to carry it out to its fullest extent; and if our science of anatomy is to grow into greater proportions and more intimate knowledge of growth, development, and *function*, its artistic expression must grow with it.

I well remember when a young medical student looking with longing eye at a fine copy, beautifully bound, of Sir Charles Bell's "System of Dissections" displayed in a shop window and opened at one of the most attractive plates, and having to content myself with the two-volume edition of his "Surgery" which I got for a song. And now after many years, I find myself looking at these same plates with even a greater pleasure, and an added appreciation. What is the charm? In what does the excellence consist?

We all know that with every true artist some bit of the personality flows out at the end of the pencil, which eludes us and cannot be expressed in words; but there are canons of excellence in Art, which can be expressed, and which we can apply in our estimation of an artistic work, even when it comes to the drawing of the dissected parts of a dead body. Some subjects so lend themselves to the artist's touch that a certain perfection may be attained by talent not of the first order, but when the subject lies outside the usual field, in fact, seems the farthest removed from any artistic treatment, it requires a higher order of talent or genius itself to bring it within the confines of Art. And it is wonderful how genius can do this for us. The real secret is, that it brings the dead to life; that in the dead body, it suggests or makes us see the life which has flown; that in the dissected arm, with the muscles and blood vessels bared, we see these muscles alive and functioning. This is the magic of Art; this is the great deception. The mere faithful copyist cannot do this.

The artistic talent of Sir Charles expressed itself in many ways. He used the pencil and the brush, he modeled in wax and plaster, and etched and engraved. He wished through the wax to catch and hold the colors of fresh pathological specimens, and to-day we are striving to do this very thing. I have not seen any of this work; there must be specimens of it somewhere in England.

According to a note in the "Letters," his sketches of the wounded at Waterloo he afterwards reproduced in water-colors, excelling in force and effect any professional paintings hitherto attempted. Many of them, together with some in oil, are now, along with those in the Windmill Street Museum, in the College of Surgeons, Edinburgh, and others in University College, London. Seventeen were presented by his widow, in 1867, to the Royal Hospital, Netley, along with his note book. In the Middlesex Hospital he made many drawings of cancer cases, but they seemed to him so distressing to look upon, he could not bear to publish them. This has always seemed strange to me.

It is interesting to note that his earliest published work, his "System of Dissections," was one of his most pretentious, and in many ways fully characterizes his qualities as an illustrator of anatomy. The drawings show a nice selection of the subject, the point of view from an artist's standpoint, the relationships of the parts with their relative values, and a skillful drawing of the different layers to show depth. There is no hesitation in the drawing; he seems always sure of the form; and whenever the subject admits it, you are aware of the feeling, a fine sentiment always, with touches of local color and surroundings to give a dramatic interest to the composition.

In Plate I, for example, in drawing the abdominal muscles, he has not only shown us the three layers, but the muscles which come into relationship with them, and he has so placed his subject that these muscles are made prominent and are seen to best advantage; and he has drawn for us the dead body itself. It lies stretched out before us with the extended arms, the set features, the relaxed jaw and staring eyes, well drawn and most striking; and yet there is nothing repulsive. The dead body itself has become of interest, and we ask involuntarily, "what manner of man was he?" It attracts and holds the attention. This is the dramatic element, which the true artist will always introduce, when possible. It has been discarded in modern anatomical drawing, and, I think, to its detriment.

In Plate VI he has drawn the open chest, with the heart and lungs in situ. Cutting through the costal cartilages he has turned back the sternum, showing the anterior mediastinal space better than I have seen it in any modern anatomy, and he brings out besides the courses of the internal mammary artery and the phrenic nerve in a way to impress them forever on the memory. The drawing is beautiful and striking; with the eye of the anatomist and the eye of the artist, he has chosen the true point of view, which the artist, by the way, is less apt to miss than the mere anatomist, no matter how well he can name the parts. I showed a drawing of the

shoulder girdle by John Flaxman to an anatomist recently, and he remarked "I never quite saw the clavicles before." It was all the point of view.

Plate XV, showing the femoral and its branches with the nerves on the anterior face of the thigh, is quite the perfection of anatomical drawing—certainly for showing the course of an artery and its deep branches—with the rest of the limb in outline, drawn with faint precision, without one unnecessary line. With consummate skill he shows us the relationship between the anterior crural nerve and the branches of the femoral, and the obturator nerve picked up by a tenaculum. When Sir Charles dissected this thigh, he not only made a skillful dissection, but he saw the true significance of the parts and gave them an artistic expression. This was his genius. To him the dead body was always alive and the impulse to draw it, whole or dissected, was as strong as the impulse to "frisk it" when he heard lively music. The drawing pencil was constantly in his hand and his drawings are legion; and I doubt not many a fine one worthy of reproduction lies hidden away somewhere in this great little island.

This work, begun in 1799, was completed in 1803, and at the same time he was making dissections and drawings for his three works on the anatomy of the brain, of the nerves, and of the arteries—work done well before he was thirty. Of his work on the arteries I have already spoken; of the plates on the nerves, we have good evidence of his skillful dissection and faithful copying from his subject, for he has drawn the courses of the nerves in delicate lines to their finer ramifications, with the flaccid and widely separated muscles consequent on nerve dissection.

With the modern anatomies before me, and the great advancement in the minute anatomy of the brain, I must confess to the charm and fascination of his plates. Though more than a century has passed, their delicate coloring still holds. But more than that, you see his comprehensive grasp of structure and how skillfully he brought it out. He reproduces but one plate from an outside source, one of the base of the brain, with the twelve cerebral nerves, from Vic d' Azyr, a bit of anatomy he was afterwards to work out so carefully and to draw for us in his own inimitable way.

And this prompts the observation how wholly his own his illustrations are, and entirely uninfluenced by outside sources. If he copies an old plate it is for its historical value. His treatment, his point of view, is his own always; and like his brother John, he never published a work which was not all himself.

When Sir Charles went to London in 1804, he carried with him the manuscript of his "Essays on the Anatomy of Expression," the illustrations for which were to show his ability to give expression to the emotions in portraiture. In the first edition, we find a number of little sketches, showing great facility in drawing as well as a keen sense of the delicate shades of facial expression; but quite aside from the merits of the illustrations, both the drawings and the text bring us face to face with the man. However excellent anatomical drawings may be, and individual too, in a way, they cannot reflect the personality of the artist like a work dealing with the emotions and passions described as well as drawn. This work Sir Charles labored many years to perfect in the succeeding editions; he eliminated much that appeared in the first edition of 1806, and added more, and labored long to make his drawings what he wished them to be; and in doing all this, he laid bare his own nature with an unconscious abandon. In no other of his works, with the exception of his published letters, do we have revealed to us the man himself—his enthusiasm, his deep insight into structure and function, his general artistic sense and love of the beautiful, his sensibility to the moral and religious in life and art, and finally, a delicate and refined sentiment which pervades all his writings and all his drawings which can give an expression of this feeling. Mere intellectual brightness and smartness seem common enough, but real sentiment, in its best sense, is much less common. It draws a halo around the seeming commonplace; it gives an added push to enthusiasm; it gives a charm even to the drawings of the dissected body. With all our hard facts, let us cultivate sentiment and let us rejoice when we find it in a man of science. Only an artist of a fine and delicate sentiment would have drawn for us the face of the laughing child which closes the introduction to this work.

After Sir Charles went to London, though he carried on with equal assiduity his anatomical researches and his lectures on anatomy, his published drawings were chiefly to illustrate pathology and surgery and the incidents of the clinic. Many figure drawings of patients in the hospital are full of expression and sentiment, and you feel at once they are true to the life, and veritable portraits. He made many of these sketches at Portsmouth, after the battle of Corunna, and in Brussels, after the battle of Waterloo, and Baron Larrey, years later, recognized many of them on a visit to London. He conceived the idea of elaborate paintings and portraits, showing the patient and the disease. This seems to me a great idea. We may well take it up, for I see ahead the time when the advanced stages of malignant disease will be a rarity indeed, will pass away, in fact, and the medical historian will have to search past records to find the clinical features of inoperable cancer. They will be prized like the portraits of an extinct race. Many of his figure drawings, though mere outlines, showing malignant tumors, are of greatest value. His brother John had this gift of rapid sketching; but he was more inclined to complete the picture. One of his sketches, however, seems to me to surpass anything of Sir Charles's as evidence of deep feeling. It is his sketch of the case of Alexander Macdonald, evidently sarcoma of the arm.* Quite aside from its scientific value, he has made its pathos beautiful, a classic face of long suffering, and the disheveled hair almost like a wreath of laurel for the heroic fight of a brave spirit with death. The young man was dying when he made this sketch. He has brought a malignant tumor within the confines of Art, and no amount of mere skill in drawing can do this alone.

*The Principles of Surgery, by John Bell. London, 1808. Vol. 3, p. 82.

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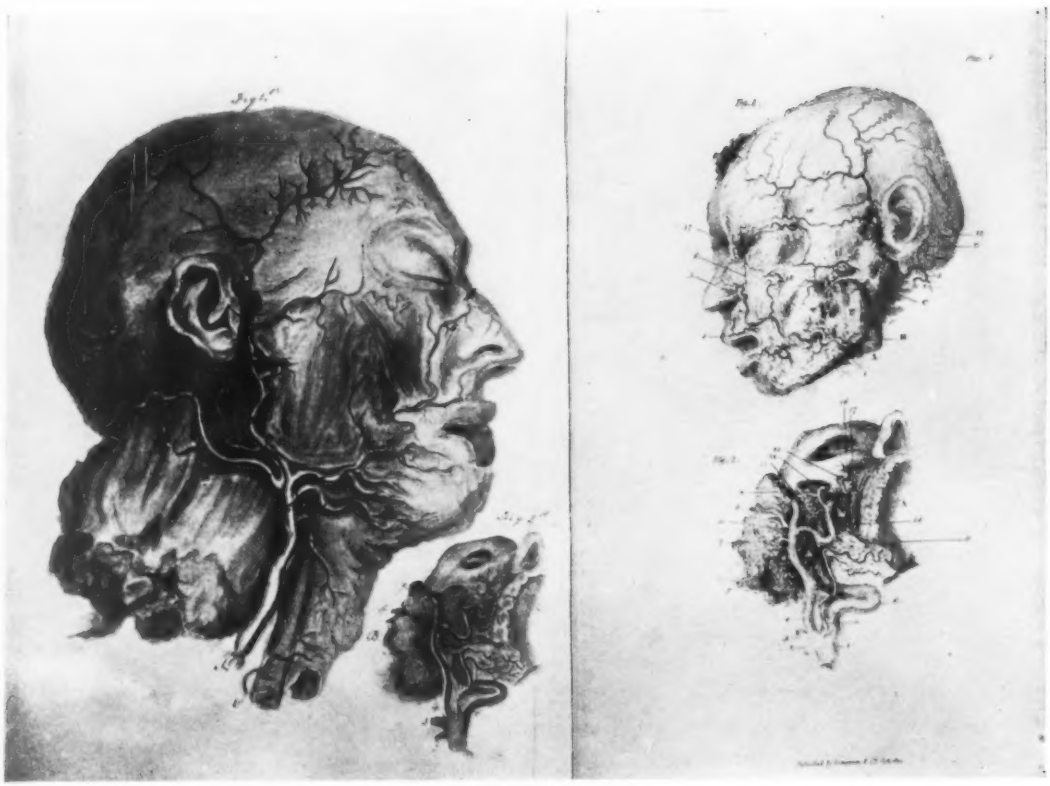
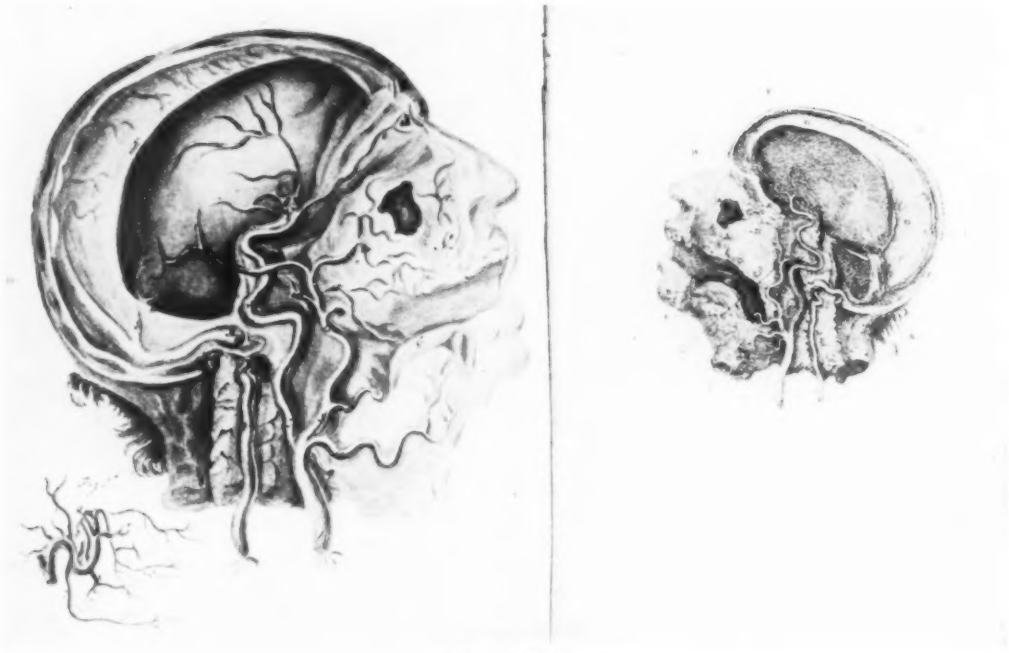
"PLATE IV."



"PLATE V."



"PLATE VI."

I cannot emphasize too strongly the value of these clinical sketches. Entering the hospital one morning he comes to a case of dislocation of the head of the femur and near by, one of fracture of its neck; and he draws for us most skillfully the clinical features; shortening, rigidity, and inversion of the foot in the one; eversion, shortening, and preternatural mobility in the other; we have nothing in modern illustration quite so good.

He conceived the idea of elaborate and artistic drawings of operations, and carried it out beautifully, drawing instruments in situ and the operative hand at work, or indicating the objective point of the operation. In his "Surgery" especially, are many of these little sketches in outline, always with an expressive hand holding an instrument, and showing at a glance what it would take a page to describe.

Though Sir Charles did so much for artistic delineation in anatomy and medicine, and wrote so much on the value of anatomy to the artist, it is only in passing reference and hints in his letters that he has anything to say of the application of Art to anatomy and medicine, to us at least, a much more important subject. He did think anatomy of great use to the artist, both in painting and statuary, and he has given us strong reasons for his belief. In this he went further than his brother John, who, while admitting its value, considered it rather limited and sharply defined; unless controlled by genius, the anatomy was apt to become too conscious a part in the conception and execution. But a great book is yet to be written on the value of Art to anatomy and medicine. Choulant * * * in his admirable work on the history of anatomical delineation down to 1850, has done much in an historical and bibliographical way to show the advances from ignorance and fancy to the true copying from nature; but the real application of the principles of Art to anatomy, and all it will mean in the future development of that science awaits its expounder. Certainly if we are to attract artists to anatomical studies, the anatomy itself should be treated from an artistic standpoint. We must bring Art to anatomy before we carry it to the artist; they can be made reciprocal. But the greatest influence of Art applied to anatomy will be in its teaching, and in making this teaching most effective. A study of mere form or structure without its life is the most barren of all studies. He who sees the form without the life back of it, sees nothing; and the more we make the form give expression to its life, the more truly artistic it becomes.

The time must come when the dissecting room will offer not only the dead body for dissection, but will help show in every way, the life of its parts. Dissecting the muscles of an arm, the student will have by him the well developed arm of the athlete to show the muscles alive.*

Sir Charles, as I have said, conceived the idea of anatomical delineation on a grand scale, but only partially attempted to carry it out. If we can get an Abbey to paint for us the Holy Grail, let us have an equally great artist paint for us the dissected body, that we may best grasp its life. It would be a great stimulus to anatomical study. Only then will our anatomy become truly significant; only then shall we have a real artistic anatomy; and then what seemed commonplace will become interesting and even beautiful.

The genius of Sir Charles Bell was towards this end; it was his genius to discern the function back of the form, and with a confident and ready hand to draw for us what he saw. He had the artistic sense of proportion, of relationship, of relative values, of the point of view; and with it all that delicate and beautiful sentiment which colored his life as well as his art. It was indeed Goethe's *milde Macht* and the *Sweetness and Light* of Matthew Arnold.

A. John Bell's sketch of the case of Alexander Macdonald showing the artistic drawing of a malignant tumor, evidently sarcoma.

PLATE 4.—Drawing of a dissection of a negro's head, showing the external carotid and its branches. It shows the free brush work. In the etching we see the more careful working up of details and a better drawing of the artery. Reduced about one-third.

PLATE 5.—Drawing and etching showing the arteries of the face. The drawing is much superior. The etching seems to be made from a different sketch. Reduced about one-third.

PLATE 6.—Drawing and etching showing the internal and external carotid, and vertebral arteries. The drawing and etching show many differences; the drawing is much more effective. Reduced about one-third.

*Geschichte and Bibliographie der anatomischen Abbildung, nach ihrer Beziehung auf anatomische Wissenschaft und bildende Kunst, von Dr. Ludwig Choulant. Leipzig, 1852.

*Sir Charles had this very idea and carried it out in a way in his lectures. (See a paper by Dr. W. W. Keen in the Transactions of the 7th International Medical Congress, 1881, "On the Systematic Use of the Living Model as a Means of Illustration in Teaching Anatomy.") The best modern work which has come to my notice, which treats of artistic anatomy with a living model, is Kollmann's "Plastische Anatomie des menschlichen Körpers für Künstler und Freunde der Kunst, von Dr. Julius Kollmann. Leipzig, 1910.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice; abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXV is now in progress. The subscription price is $2.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, $2.50 each.

A complete index to Vol. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

NOTES ON NEW BOOKS.

Social Work in Hospitals: A Contribution to Progressive Medicine. By IDA M. CANNON, R. N. $1.50. (*Survey Associates, Inc., Publishers for the Russel Sage Foundation.*)

There is no one so well qualified as Miss Cannon to interpret the uses of hospital social service, not only by reason of the study she has made of the subject, but because she has put so much of herself into the movement and has been so live an influence in its development.

Miss Cannon's is the first text-book on social work in hospitals that has been published, and though she feels that notwithstanding the widespread interest in the movement it is of too recent date and the experience gained of too experimental a nature to justify the laying down of dogmatic rules, either as to the function of the social worker or the proper organization of the work; still she points to certain ideals that have developed and fundamental principles that have been evolved.

She follows the history of hospital social service from the beginnings, referring to the social work of the medical students at The Johns Hopkins Hospital, under Dr. C. P. Emmerson, as one of the four important contributions towards the development of the movement, through its various phases and problems to the future ideals and possibilities. The book is full of helpful suggestions, dwelling upon the importance of thorough social training and efficiency and pointing out the dangers and pitfalls consequent upon poor standards. She puts before us, in a convincing manner, the interdependence of medical and social diagnosis and treatment.

Miss Cannon's book is a constructive piece of work that should be read by those interested in hospital management as well as by physicians, nurses and social workers.

Lectures on Tuberculosis to Nurses. OLLIVER BRUCE, M. R. C. S., L. R. C. P. $1. (*New York: Paul B. Hoeber, 1913.*)

This book is "based on a course of lectures" delivered to the Queen Victoria Jubilee Nurses. The value to nurses of a description in detail of opsonic index technic, also of methods of physical examination of patients is questionable. The opsonic index is mentioned too often throughout the work, considering the present views of any value it may have in tuberculosis work.

Such a course of lectures would be of benefit to a junior medical student, but can hardly be useful as a standard for nurses.

Diseases of the Digestive Canal. By DR. PAUL COHNHEIM. Edited and translated by DUDLEY FULTON, M. D. Illustrated. Third edition. $4. (*Philadelphia and London: J. B. Lippincott Company, 1914.*)

That the profession have recognized the value of Cohnheim's work is indicated by the fact that the publishers have brought out a new edition, which varies but slightly from its predecessor. It is a well written, helpful book for students and general practitioners.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, M. D. Seventh edition. Revised and enlarged. $4.50. (*Philadelphia and London: W. B. Saunders Company, 1913.*)

The author has added five thousand terms to his previous edition, and his work continues to grow in value, and with each new issue its popularity will become greater. With the active growth in medical and allied sciences such a dictionary becomes absolutely essential to all students, and Dr. Dorland's can be recommended most heartily.

The Surgical Clinics of John B. Murphy, M. D. (December, 1913.) Published Bi-Monthly. (*Philadelphia and London: W. B. Saunders Company.*)

The majority of the papers in this number deal with bone lesions, and are well illustrated by X-ray photographs. Those anxious to learn how Dr. Murphy conducts a students' clinic will secure a good impression of his manner and style by reading the concluding paper in this issue of the "Clinics."

Oxford Medical Publications: Manual of Surgery. By ALEXIS THOMSON and ALEXANDER MILES. Vol. III. Operative Surgery. Second edition. Illustrated. $3.50. (*London: Henry Frowde and Hodder & Stoughton, 1913.*)

This Edinburgh surgery is one that must appeal to many students and operators. The text is concise, simple, and practical, and the illustrations clear and well chosen. The authors are acquainted fully with the work done in foreign clinics, and their manual is, to put it simply, excellent.

A Text-Book of Physiology for Medical Students and Physicians. By WILLIAM H. HOWELL, M. D., etc. Fifth edition. Thoroughly revised. $4. (*Philadelphia and London: W. B. Saunders Company, 1913.*)

No fresh word of commendation is needed for this famous classic. To every real student a new edition of this book is a true pleasure; and it is a source of infinite satisfaction to him to have Dr. Howell's views on the latest work along physiological lines.

Practitioners' Visiting List. $1.25. (*Philadelphia and New York: Lea & Febiger, 1914.*)

The publishers have issued an attractive book, well suited to the needs of many practitioners. It is furnished with a large variety of tables to which reference is frequently useful. The "List" is practically arranged, convenient, and neat in appearance.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D. Assisted by LEIGHTON F. APPLEMAN, M. D. Vol. IV. December, 1913.

This volume contains reviews of diseases and surgical conditions of many of the abdominal organs, and of the surgery of the extremities and tumors, and of such problems as anæsthesia, shock and infections. The need of "Progressive Medicine" is distinct, and the publication is prepared with ability and thoroughness, so that it is of real value to the majority of the medical profession.

Pyorrhea Alveolaris. By FRIEDRICH HECKER, M. D. $2. (*St. Louis: C. V. Mosby Company, 1913.*)

The author is a dentist as well as a physician, so that he has had ample opportunity to become acquainted with this disease, but it is to be feared that he is on the wrong track in attempting to distinguish eleven different varieties of this affection. Further study will probably show that this classification can be much simplified when the causative organism is finally distinguished. The pathological illustrations are marred by the lettering, and the book adds nothing to what is already known about this disease.

Chloride of Lime in Sanitation. By ALBERT H. HOOKER. (*New York: John Wiley & Sons, 1913.*)

This little book of some 200 pages contains an excellent historical account of the development of our knowledge of the chemistry of the chloride of lime of which calcium hypochlorite,

$CaOCl_2$, is the active disinfecting agent, together with elaborate directions for its practical use. The extent to which this disinfectant is being employed is well illustrated by the rather voluminous literature cited. It should prove of great value to practical sanitarians.

Causes and Cures of Crime. By THOMAS SPEED MOSBY. (*St. Louis: C. V. Mosby Company, 1913.*)

Mr. Mosby is a lawyer and a former pardon attorney of the State of Missouri. He has seen many criminals, and read widely, judging from numerous extracts in this volume, on penology, but he has compiled a work quite elementary in character and one which offers no new suggestions to the real student of this subject. The photographs of criminals inserted here and there in the volume are not helpful to the reader, for there is no reference to them in the text.

London Medical Publications: The Principles and Practice of Medical Hydrology. By R. FORTESCUE FOX, M. D. (London). (*London: University of London Press.*)

Medical hydrology or hydrotherapy is a subject not so well understood, either by doctors or nurses, as it should be, and here is a book on this method of treatment which is distinctly helpful It is not a profound treatise on hydrotherapy, but a clearly written guide book covering the essentials in a simple and satisfactory manner. It is divided into four parts: 1, The Physiology of Bathing; 2, Hydrotherapy; 3, Medicinal Springs and Baths; and 4, Indications for Hydrological Treatment.

The Diseases of Children. By HENRY ENOS TULEY, M. D. Second revised edition. (*St. Louis: C. V. Mosby Company, 1913.*)

This book now appears in its second edition and consists of 597 pages. Many chapters have been rewritten, and a few illustrations have been added. In the appendix, the Standards and Methods for the production of Certified Milk as adopted by The American Association of Medical Milk Commissions are given. These standards are chiefly of interest to the producer of milk and from the point of view of the reviewer add but little to the value of the book for students and practitioners. The present day tendency is toward simpler methods in the feeding of infants. The complicated formulæ for the modification of milk found in the appendix are not only of questionable value but are confusing to one desirous of obtaining practical information along this line. Their use should not be advised. The text is written with a disregard for the proper English construction of the sentences and in many instances authenticity for the statement of facts is lacking. By way of illustration, on page 275, the author says, "In no class of cases does a complete climatic change have so beneficial an action as in children convalescing from enterocolitis. From points south of Mason and Dixon's Line, no other change is more beneficial than removal to points in Michigan. The large amount of water through this state imparts a life-giving something to the air which works wonders in these cases." Many of the illustrations are poor and unnecessary. Some of them (pages 101, 102, 110) may be of interest to the agriculturalist and to the producer of milk, but scarcely to students of medicine. The book which is intended for the student and the general practitioner does not fulfill its purpose satisfactorily.

Treatment of Tuberculosis. By ALBERT ROBIN, M. D. Translated by LÉON BLANC, M. D. $5.25. (*New York: The Macmillan Company, 1913.*)

This work of 600 pages is the first English edition translated from the French by Dr. Léon Blanc.

The author deals with the subject from two main standpoints: the soil and the germ, and emphasizes greatly the question of the soil. His contention, "contagion is not all in all in tuberculosis," is made unnecessarily emphatic, as predisposition in general is a fact recognized by the profession.

It is claimed that great reliance should be placed on drug medication in treatment. This is not in accordance with the view generally held, and the author fails to prove his claim.

Tuberculin is given scant praise, and such a statement as "the greater the gravity of tuberculosis the weaker should be the initial dose," is mystifying, and even if true would require some explanation of proof.

Altogether the book is only fair. It is written for the general practitioner and some of the matter could be taken out without lessening the value of the work.

The translation is very good—the English being good and easily readable.

International Clinics. Vol. IV. 23d series. $2. (*Philadelphia and London: J. B. Lippincott Company, 1913.*)

Medicine, surgery and neurology are well represented in the "Clinics." Some of these are too long, but the papers by Warthin, Sewall, and Proescher are among the best in the volume. Some of the more modern views in neurology are presented in one or two papers, and eugenics is abused by having two articles attributed to it, which would be better classified under some other heading. The term eugenics is generally misunderstood and misapplied by American writers.

Cunningham's Text-Book of Anatomy. Edited by ARTHUR ROBINSON, M. D., F. R. C. S., Ed. Fourth edition. Enlarged and rewritten. Illustrated. $6.50. (*New York: William Wood & Co., 1913.*)

From the title one would naturally infer that this work was like Gray's, that is, the writing of one anatomist; on the contrary, it is the reverse, there being for this last edition eleven contributors, all Englishmen, and there is, what is more striking, no chapter by Cunningham. But as he was the originator of this compilation it still partly bears his name and is one of Gray's chief competitors in the medical schools, which is an honor in itself, since the anatomy by Gray is conceded to be unsurpassed in English as the work of a single author. Cunningham's Text-Book in its new form is undoubtedly a book that will appeal to students for it is very liberally illustrated, uses the B. N. A. nomenclature, has an admirable index, and the text has been carefully revised and is modern.

A Practical Treatise on Medical Diagnosis for Students and Physicians. By JOHN H. MUSSER, M. D., etc. Sixth edition. Revised by JOHN H. MUSSER, JR., M. D. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1913.*)

So many additions of various sorts have ben made to the methods of medical diagnosis since eight years ago when the last edition of Musser appeared, that it was essential, if his excellent work were to continue useful, that it be brought up to date. This has been done by his son, who has found it necessary to revise largely his father's book by additions and eliminations; but in general scope and character this treatise retains its original character which all who knew the elder Musser value for his sake.

A Manual of X-Ray Technic. By ARTHUR C. CHRISTIE, Medical Corps, U. S. A. Illustrated. $2. (*Philadelphia and London: J. B. Lippincott Company.*)

The clear and concise descriptions throughout the book, especially those pertaining to the electro-mechanics of X-Ray, well merit popularity, and to the man who is just "starting" Roentgenology the work should be a help.

Aside from this the reader will gain little, as the methods of interpretation and diagnosis are too brief and hardly abreast of the times. Roentgentherapy is not discussed.

Disease and Its Causes. By W. T. Councilman, A. M., M. D., LL. D. (*New York: Henry Holt & Co., 1913.*)

This little volume published in a series known as the Home University Library of Modern Knowledge, should serve the useful purpose of giving the laity reliable information concerning the topic with which it deals. In about 250 pages Dr. Councilman defines disease and describes its extrinsic and intrinsic causes. A large portion of the book is devoted to a discussion of the infectious diseases, though other organic diseases, especially diseases of the heart, are briefly dealt with. The subject of insanity is also discussed and the relations of degeneracy and criminality to states of the nervous system touched upon. In the last chapter of the book the relation of modern conditions of life to the extension of disease is taken up.

We do not know of any other small volume in which the layman can find such a mass of information so clearly and attractively presented concerning the matters with which modern medicine has to deal.

Oxford Medical Manuals: The Elements of Bandaging, Fractures and Dislocations. By William Rankin, M. B. $1.50. (*London: Henry Frowde and Hodder & Stoughton, 1913.*)

It is a small volume of 115 pages, with numerous illustrations and large type, so that the volume could be read easily in an hour. The three subjects discussed cannot be satisfactorily covered in such small compass, and it is to be regretted if the information contained is sufficient to prepare men "for the practical portion of their final examination."

Oxford Medical Publications: The Practitioner's Practical Prescriber. By D. M. Macdonald, M. D. $1.50.

Practical Presenting with Clinical Notes. By Arthur H. Prichard, M. R. C. S., etc. $2. (*London: Henry Frowde and Hodder & Stoughton, 1913.*)

The first of these works is nothing more than a small pocket formulary to which is appended a table of dosage, brief directions for common emergencies, a pregnancy table, etc. The work is similar to many others, and will be useful to those who like this class of work.

Prichard's book is novel in its mode of presentation. He supplies a number of prescriptions, explains them by "giving, by way of explanatory notes, reasons for employing the various constituents, their particular actions, and any special points concerning them. . . . . to illustrate the effects of the various drugs in combination a number of illustrative cases have been epitomized. The results of treatment in these are indicated in short notes, while the main features of each case are briefly summed up by way of comment." The author arranges his remarks and clinical notes in parallel columns, and in this small volume he can only cover a limited field, but the method is one with distinct advantages, as it makes more vivid than usual the effect of drugs on patients. Though it is more adapted to the bedside than to book form, yet a good student will gain much from a careful reading of "Practical Presenting."

A Text-Book of Histology. By Dr. Frederic T. Lewis and Dr. Philipp Stöhr. Second edition. Illustrated. $3. (*Philadelphia: P. Blakiston's Son & Co., 1914.*)

A Text-Book of Histology. By Frederick R. Bailey, M. D. Fourth revised edition. Illustrated. $3.50. (*New York: William Wood & Co., 1913.*)

Stöhr's famous and most widely read work appears completely revised and much rewritten by Lewis, and it remains to be seen whether in its new form it will be as popular in the future as in the past. It is arranged upon an embryological basis, and as embryology now plays a much more important rôle in the medical curriculum than a few years ago, Lewis' book will be helpful for the student in association with his general anatomy.

The other histology, by Bailey, familiar to and liked by many students, will appeal readily to many more just beginning their study of medicine to whom it is well adapted by its clear style and simplicity.

The Practice of Medicine. By James Tyson, M. D., etc., and M. Howard Fussell, M. D. Sixth edition. Revised and rewritten. Illustrated. (*Philadelphia: P. Blackiston's Son & Co., 1914.*)

The new edition has been abridged in parts and enlarged in others, causing imperfections as well as perfections. It is a pity that all the historical part of the subject had to be omitted, and also that the section on parasites, which are becoming more and more important in the study of medicine, had to be shortened. The work is more complete in having fuller accounts of some old diseases, and by the introduction of some diseases which are rare and not always included in all text-books of medicine. Otherwise this standard work remains unaltered, and noteworthy as the production of one of Philadelphia's eminent practitioners. The index is unfortunately incomplete; there is no reference, at least we could not find it, to phenosulphonephthalein, and yet this is mentioned as one of the important new subjects in the preface.

BOOKS RECEIVED.

Radium. As Employed in the Treatment of Cancer, Angiomata, Keloids, Local Tuberculosis and Other Affections. By Louis Wickham, M. V. O., and Paul Degrais. Translated by A. and A. G. Bateman, M. B., C. M. With fifty-three illustrations. 1913. 12°. 111 pages. Paul B. Hoeber, New York.

Modern Problems of Biology. Lectures delivered at the University of Jena, December, 1912. By Charles Sedgwick Minot. With fifty-three illustrations. 1913. 8°. 124 pages. P. Blakiston's Son & Co., Philadelphia.

Cancer of the Breast. An Experience of a Series of Operations and Their Results. By Charles Barrett Lockwood, F. R. C. S. (Eng.). 1913. 8vo. 234 pages. Henry Frowde, London; Hodder & Stoughton, London.

Treatment of Tuberculosis. Ordinary Therapeutics of Medical Men. By Albert Robin. Translated by Dr. Léon Blanc, with the assistance of H. de Méric. 1913. 8vo. 616 pages. The Macmillan Company, New York.

A Manual of Surgical Treatment. By Sir W. Watson Cheyne, Bart., C. B., D. Sc., LL. D., F. R. C. S., F. R. S., and F. F. Burghard, M. S. (Lond.), F. R. C. S. New edition, entirely revised and largely rewritten with the assistance of T. P. Legg, M. S. (Lond.), F. R. C. S., and Arthur Edmunds, M. S. (Lond.), F. R. C. S. Volume V. *The Treatment of the Surgical Affections of the Pancreas, Liver and Spleen, the Neck, the Breast and Thorax, and the Genito-Urinary Organs.* 1913. 8vo. 619 pages. Lea & Febiger, Philadelphia and New York.

Artificial Parthogenesis and Fertilization. By Jacques Loeb. Originally translated from the German by W. O. Redman King, B. A. Supplemented and revised by the author. [1913.] 8°. 312 pages. The University of Chicago Press, Chicago.

The Ideals and Organisation of a Medical Society. By Jamieson B. Hurry, M. A., M. D. 1913. 8°. 51 pages. J. & A. Churchill, London.

Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M. D., F. R. S., and Thomas McCrae, M. D. Volume I. Second edition, thoroughly revised. Illustrated. 1913. 8°. 1093 pages. Lea & Febiger, Philadelphia and New York.

The Unexpurgated Case against Woman Suffrage. By Sir Almroth E. Wright, M. D., F. R. S. [1913.] 12°. 188 pages. Paul B. Hoeber, New York.

A Manual of X-Ray Technic. By Arthur C. Christie. With 42 illustrations. [1913.] 8°. 104 pages. J. B. Lippincott Company, Philadelphia and London.

Science and Education. A Series of Volumes for the Promotion of Scientific Research and Educational Progress. Edited by J. McKeen Cattell. Volume II. *Medical Research and Education.* By Richard M. Pearce [and others]. 1913. 8°. 536 pages. The Science Press, New York and Garrison.

The Principles and Practice of Medical Hydrology. Being the Science of Treatment by Waters and Baths. By R. Fortescue Fox, M. D. (Lond.); F. R. Met. Soc. 1913. 8°. 295 pages. University of London Press, London.

Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

1. *The Practitioner's Practical Prescriber and Epitome of Symptomatic Treatment.* By D. M. Macdonald, M. D. 1913. 16°. 198 pages.

2. *The Elements of Bandaging and the Treatment of Fractures and Dislocations.* By William Rankin, M. A., M. C., Ch. B. With sixty-eight original illustrations. 1913. 12°. 116 pages.

3. *Practical Prescribing with Clinical Notes.* By Arthur H. Prichard, M. R. C. S., L. R. C. P., R. N. (Rtd.). 1913. 12°. 307 pages.

4. *Defective Ocular Movements and Their Diagnosis.* By E. and M. Landolt (Paris). Translated by Alfred Roemmele, M. B., Ch. B., and Elmore W. Brewerton, F. R. C. S. 1913. 8vo. 97 pages. Oxford University Press, American Branch, New York.

5. *Coxa Vara, Its Pathology and Treatment.* By R. C. Elmslie, M. S., F. R. C. S. 1913. 8vo. 35 pages. Oxford University Press, American Branch, New York.

6. *Manual of Surgery.* By Alexis Thomson and Alexander Miles. Volume third. *Operative Surgery.* Second edition. With 255 illustrations. 1913. 12mo. 620 pages. Oxford University Press, American Branch, New York.

7. *Dysenteries, their Differentiation and Treatment.* By Leonard Rogers, M. D., F. R. C. P., B. S., F. R. C. S., C. I. E., I. M. S. 1913. 8°. 336 pages.

8. *Surgical Experiences in South Africa, 1899-1900.* Being Mainly a Clinical Study of the Nature and Effects of Injuries Produced by Bullets of Small Calibre. By George Henry Makins, C. B., F. R. C. S. Second edition. 1913. 8°. 504 pages.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. Assisted by Leighton F. Appleman, M. D. Volume IV. December, 1913. 8°. 411 pages. Lea & Febiger, Philadelphia and New York.

Year-Book of the Pilcher Hospital. For the Period from April 1, 1912, to March 31, 1913. Being the Third Year of the Operation of the Hospital. 8vo. 178 pages. Brooklyn, New York.

Pyorrhea Alveolaris. By Friedrich Hecker, B. Sc., D. D. S., A. M., M. D. Illustrated, 1913. 12°. 157 pages. C. V. Mosby Company, St. Louis.

Causes and Cures of Crime. By Thomas Speed Mosby. Illustrated. 1913. 12°. 354 pages. C. V. Mosby Company, St. Louis.

Diseases and Deformities of the Foot. By John Joseph Nutt, B. L., M. D. Illustrated. 1913. 8°. 293 pages. E. B. Treat & Company, New York.

Die körperliche Erziehung des Kindes. Von Prof. Dr. Hans Spitzy. Mit 194 Textabbildungen. 1914. 8vo. 416 pages. Urban & Schwarzenberg, Berlin und Wien.

Modern Problems in Psychiatry. By Ernesto Lugaro. Translated by David Orr, M. D., and R. G. Rows, M. D. With a Foreword by Sir T. S. Clouston, M. D., LL. D. 1913. 8°. 305 pages. At the University Press, Manchester.

Transactions of the American Urological Association. Twelfth Annual Meeting at Boston, Massachusetts, April 15, 16 and 17, 1913. Vol. VII. 1913. 8°. 285 pages. Riverdale Press, Brookline, Mass.

Handbuch der Neurologie. Herausgegeben von M. Lewandowsky. Vierter Band. Spezielle Neurologie, III. Mit 56 Textabbildungen. 1913. 8°. 493 pages. Julius Springer, Berlin.

Die Erkrankungen der Blutdrüsen. Von Dr. Wilhelm Falta. Mit 103 Textabbildungen. 1913. 8°. 550 pages. Julius Springer, Berlin.

Die biologischen Grundlagen der sekundären Geschlechtscharaktere. Von Dr. Julius Tandler und Dr. Siegfried Grosz. Mit 23 Textfiguren. 1913. 8°. 169 pages. Julius Springer, Berlin.

Disease and its Causes. By W. T. Councilman, A. M., M. D., LL. D. [1913.] 16°. 254 pages. Henry Holt and Company, New York; Williams and Norgate, London.

American Red Cross Textbook on Elementary Hygiene and Home Care of the Sick. By Jane A. Delano, R. N., and Isabel McIsaac, R. N. Prepared for and indorsed by the American Red Cross. 1913. 12°. 256 pages. P. Blakiston's Son & Co., Philadelphia.

Diätetik innerer Erkrankungen zum praktischen Gebrauche für Ärzte und Studierende. Von Professor Dr. Theodor Burgsch. 1911. 8°. 245 pages. Julius Springer, Berlin.

Handbuch der Radium-Biologie und Therapie einschliesslich der anderen radioaktiven Elemente. Herausgegeben von Prof. Dr. Paul Lazarus. Mit einem einleitenden Vorwort von Geh. Rat Prof. Dr. Friedrich Kraus. Mit 153 Abbildungen im Text und 2 Tafeln. 1913. 8°. 521 pages. J. F. Bergmann, Wiesbaden.

Die Krankheiten des Mundes. Von J. von Mikulicz und W. Kümmel. Dritte Auflage. Neu bearbeitet von Werner Kümmel. Mit Beiträgen von Prof. A. Czerny und Prof. J. Schäffer. Mit 79 zum Teil farbigem Abbildungen im Text. 1912. 8°. 320 pages. Gustav Fischer, Jena.

Lehrbuch der Nervenkrankheiten. Von Prof. Dr. H. Oppenheim. Sechste, wesentlich vermehrte und verbesserte Auflage. Mit 523 Abbildungen im Text und 14 Tafeln. Two Volumes. 1913. 8°. 1926 pages. S. Karger, Berlin.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Twenty-third Series. Volume IV. 1913. 8vo. 312 pages. J. B. Lippincott Company, Philadelphia and London.

Meningococcus Meningitis. By Henry Heiman, M. D., and Samuel Feldstein, M. D. With Introduction by Henry Koplik, M. D. 1913. 8°. 313 pages. J. B. Lippincott Company.

Cunningham's Text-Book of Anatomy. Edited by Arthur Robinson, M. D., F. R. C. S. Fourth edition, enlarged and rewritten. Illustrated by 1124 figures from original drawings, 637 of which are printed in colors, and two plates. 1913. 8°. 1596 pages. William Wood and Company, New York.

In Memory of Dr. James Livingstone Thompson 1832-1913 and His Son, Dr. Daniel A. Thompson 1862-1904. By The Indianapolis Literary Club, The Indianapolis Medical Society, The Loyal Legion of Indiana, The Medical College of Indiana, The Family of Dr. Thompson, and Other Friends and Lovers of Many Years. 1913. 12°. 98 pages. Indianapolis, Ind.

A Text-Book of Histology. By Frederick R. Bailey, A. M., M. D. Fourth revised edition, profusely illustrated. 1913. 8vo. 644 pages. William Wood and Company, New York.

Cancer, Its Cause and Treatment without Operation. By Robert Bell, M. D., F. R. F. P. S., etc. Second edition, revised. 1913. 12°. 324 pages. G. Bell and Sons, Ltd., London. The MacMillan Company, New York.

Surgery of the Upper Abdomen. In two volumes. By John B. Deaver, M. D., Sc. D., LL. D., and Astley Paston Cooper Ashhurst, A. B., M. D. Volume II. *Surgery of the Gall-Bladder, Liver, Pancreas and Spleen.* With 52 illustrations. 1914. 8°. 499 pages. P. Blakiston's Son & Co., Philadelphia.

A Text-Book of Histology. Arranged upon an Embryological Basis. By Frederic T. Lewis and Dr. Philipp Stöhr. Second edition, with 495 illustrations. Being the seventh American edition of Stöhr's Histology. From the fifteenth German edition, edited by Dr. O. Schultze. 1914. 8°. 539 pages. P. Blakiston's Son & Co., Philadelphia.

The Practice of Medicine. A Text-Book for Practitioners and Students with Special Reference to Diagnosis and Treatment. By James Tyson, M. D., LL. D., and M. Howard Fussell, M. D. Sixth edition, revised and rewritten. With six plates and 179 other illustrations. 1914. 8°. 1211 pages. P. Blakiston's Son & Co., Philadelphia.

Scientific Memoirs. (New Series.) No. 60. By Officers of the Medical and Sanitary Departments of the Government of India. *Studies on the Mouth Parts and Sucking Apparatus of the Blood-Sucking Diptera. No. 4. The Comparative Anatomy of the Proboscis in the Blood-Sucking Muscidae.* By Captain F. W. Cragg, M. D., I. M. S. 1913. 4°. 56 pages. Superintendent Government Printing, Calcutta, India.

Cardio-vascular Diseases. Recent Advances in their Anatomy, Physiology, Pathology, Diagnosis and Treatment. By Thomas E. Satterthwaite, A. B., M. D., LL. D., Sc. D. 1913. 8°. 166 pages. Lemcke and Buechner, New York.

Stanford University. Medical Publications. Bulletin No. 1. 1913. 4°. San Francisco, California.

Diseases of the Heart. By James Mackenzie, M. D., F. R. C. P., LL. D., Ab. and Ed., F. R. C. P. I. (Hon.). Third edition. 1913. 8vo. 502 pages. Oxford Medical Publications. H. Frowde, London; Hodder & Stoughton, London.

An Introduction to the History of Medicine. With Medical Chronology, Bibliographic Data and Test Questions. By Fielding H. Garrison, A. B., M. D. Illustrated. 1914. 8vo. 763 pages. W. B. Saunders Company, Philadelphia and London.

A Text-Book of Physiology. By William H. Howell, Ph. D., M. D., LL. D. Fifth edition, thoroughly revised. 1913. 8vo. 1020 pages. W. B. Saunders Company, Philadelphia and London.

The Surgical Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Volume II, Number 6, December, 1913. 8vo. W. B. Saunders Company, Philadelphia and London.

Russell Sage Foundation. Social Work in Hospitals. A Contribution to Progressive Medicine. By Ida M. Cannon, R. N. 1913. 12mo. 257 pages. Survey Associates, Inc., New York.

Anatomy and Physiology. A Text-Book for Nurses. By John Forsyth Little, M. D. Illustrated with 149 Engravings and 4 Plates. [1914.] 12°. 483 pages. Lea & Febiger, Philadelphia and New York.

Medical and Surgical Reports, Buffalo General Hospital. Volume I. 1913. 8vo. 249 pages. Buffalo, New York.

Ergebnisse der Chirurgie und Orthopädie. Herausgegeben von Erwin Payr und Hermann Küttner. Siebenter Band. Redigiert von H. Küttner. Mit 335 Textabbildungen und 1 Tafel. 1913. 8°. 858 pages. Julius Springer, Berlin.

Lectures on Tuberculosis to Nurses. Based on a Course delivered to the Queen Victoria Jubilee Nurses. By Olliver Bruce, M. R. C. S., L. R. C. P. With illustrations. 1913. 12°. 134 pages. Paul B. Hoeber, New York.

Lectures on Medical Electricity to Nurses. An Illustrated Manual. By J. Delpratt Harris, M. D. Durh., M. R. C. S. With 23 illustrations. 1913. 12°. 88 pages. Paul B. Hoeber, New York.

The Healthy Marriage. A Medical and Psychological Guide for Wives. By G. T. Wrench, M. D., B. S. (Lond.). 1914. 12°. 300 pages. Paul B. Hoeber, New York.

The Pathology of Growth. Tumours. By Charles Powell White, M. D., F. R. C. S. Illustrated. 1913. 8°. 235 pages. Paul B. Hoeber, New York.

Materia Medica: Pharmacology: Therapeutics: Prescription Writing. By Walter A. Bastedo, Ph. G., M. D. Illustrated. 1913. 8vo. 602 pages. W. B. Saunders Company, Philadelphia and London.

Principles of Surgery. By W. A. Bryan, A. M., M. D. Original illustrations. 1913. 8vo. 677 pages. W. B. Saunders Company, Philadelphia and London.

The American Illustrated Medical Dictionary. A new and complete dictionary of the terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology, medical biography, etc. By W. A. Newman Dorland, A. M., M. D. Seventh edition, revised and enlarged. 1913. 8vo. 1107 pages. W. B. Saunders Company, Philadelphia and London.

NEW PUBLICATIONS.

The following six monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, $1.00.

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of the Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL. D., F. S. S. 161 pages. Price, $2.00.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D. In press.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.